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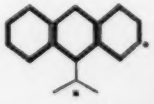

Neurology

Volume 5 *Number 12*

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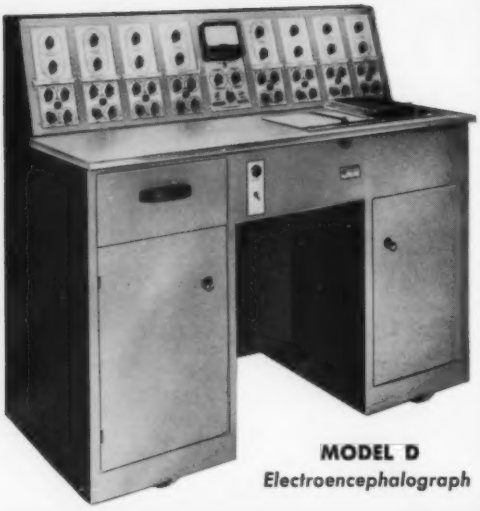

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Volume 5 Neurology *Number 12*

Changing Status of Electroencephalography in Neurologic Practice

James L. O'Leary, M.D.

DURING THE POSTWAR YEARS neurology has departed from its earlier role as an ancillary of neuropsychiatric practice, and now has its own dynamic approach and an ever present treatment goal. That change in emphasis has led to increasing rapprochement between neurologist and internist, general surgeon, surgical specialist, pediatrician, and sometimes obstetrician and anesthetist. In hospital centers a neurologist is less often called upon to place a neurologic disease in its proper category, and more often to evaluate the significance of symptoms and prescribe treatment. As the accuracy of his pathophysiologic deductions improves, his counsel is increasingly in demand. My present purpose is to consider the contributions an electroencephalographer can make in furthering this favorable trend in neurologic practice.

Indeed the trend poses many new problems for the electroencephalographer. Once, a single tracing was considered sufficient if it pointed to a diagnosis of convulsive disorder as opposed to syncope or an hysterical attack, or if it aided in locating a focal process. The electroencephalographer was able to adhere to a routine covering all of the eventualities that might develop during a single tracing. For each such tracing 20 to 40 electrodes might be placed, with recording from one-half to several hours, while the possible combinations between them were exhausted. But the number of patients thought to require an electroencephalogram is increasing steadily, serial recordings and sleep tracings are done more often, and even daily bedside checks are asked for in critical cases. Thus a brain wave tracing can no

From the division of neurology, Washington University School of Medicine, St. Louis.
Read at the seventh annual meeting of the American Academy of Neurology, Houston, Texas, April 28, 1955.

longer be a research in itself. As the electroencephalogram becomes a more irreplaceable tool of the neurologist's bag, compromises with routine are inevitable if the maximum neurologic use is to be obtained from an electroencephalographic facility.

What are some of the demands made upon the laboratory of a large hospital center? Children suspected of or diagnosed as having febrile convulsions, head injury, behavior disorder, mental retardation, hydrocephalus, toxic reaction, encephalitis, meningitis, cerebral palsy, or hypoglycemia may have one or several tracings each. A child with meningitis may have repeated electroencephalograms as therapy progresses. Increasing attention is being given to paroxysmal headaches in children. In adults headache and vertigo have been added to convulsions as symptoms in which the electroencephalogram may provide useful data. During the treatment of meningitis and in certain cerebrovascular problems, bedside checks of brain activity may indicate whether the condition is remaining stationary, improving, or deteriorating. Metabolic disorders not infrequently cause collateral central nervous system symptomatology accompanied by significant electroencephalographic alterations. The ramifications of hematology bring in a small case load. On the general surgical service central nervous system symptoms may result from a deficit in extracellular fluid or from electrolyte insufficiency. Pulmonary conditions, including neoplastic ones treatable by thoracic surgery, may suggest a survey for cerebral metastases before proceeding with lobectomy or pneumonectomy. The neurosurgeon has added to his other uses for the electroencephalogram cases of subarachnoid hemorrhage where aneurysm is suspected. The multiple symptomatology that can result from cerebrovascular aging also necessitates many electroencephalograms.

The material selected for presentation here indicates the widening application of the procedure in neurologic diagnosis.

ELECTROENCEPHALOGRAPHY IN PEDIATRIC NEUROLOGY

Studies by Gibbs and Gibbs[1] and Kellaway and Fox[2] have disposed of certain sleep and arousal patterns of the normal child tracing that may simulate convulsoid activity. These details of interpretation will not be discussed further.

Brain wave tracings of infants and children can aid materially in differentiating partial seizures of focal cortical origin from petit mal attacks, with certain reservations that relate to the respective ages at which the cortex becomes sufficiently mature to synchronize focal versus generalized (that is, 3/sec. spike and wave) patterns of discharge. In young infants recorded during generalized or hemiseizures, there may be no hint of truly synchronized paroxysmal disturbance even though the ictal tracing is slower and of higher voltage than the expectancy for age. Exceptionally focal paroxysmal transients can be detected during seizure as early as six days after birth. These, however, may not be recorded in interseizure periods before four months, and for that reason negative tracings in young infants should be repeated. The 3/sec. spike and wave which we have come to associate with petit mal attacks does not appear earlier than 16 months,[3] occurring then in its definitive form without antecedent signs.

Focal or lateralized electroencephalographic disturbance may be found in

children who have either general or focal seizures. For the neurologist each such case presents the need for deciding whether or not the seizures are determined structurally. In those instances where lateralized disturbance (continuous slow, or paroxysmal transient) is coupled with seizures originating upon the opposite side of the body, or where there is evidence of a cerebral disturbance of the motor path (as in hemiparesis), there is always a strong suspicion of underlying structural defect. One thinks first of the possibilities of intrauterine vascular mishap, perhaps associated with a congenital defect of the heart, an intrauterine infectious process, an embolus arising at the tying of the umbilical cord and passing through a still patent foramen ovale to lodge in the brain, residuals of anoxic or traumatic birth injury, and kernicterus. In other instances a violent seizure in a child, previously normal neurologically, may leave hemiparesis as a permanent deficit. The sequelae of encephalitis or meningitis may include focal seizures. Very occasionally focal paroxysmal transient (2/sec. spike wave, petit mal variant type) may relate to underlying cyst and possibly to other space-occupying pathology (figure 1).

In a hospital electroencephalographic laboratory it is not unusual to record from a stuporous child with or without

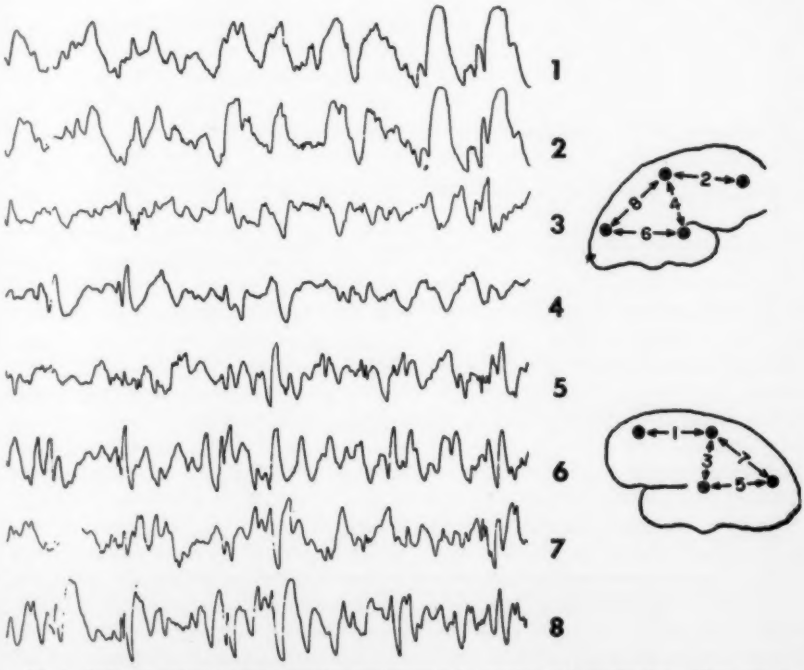
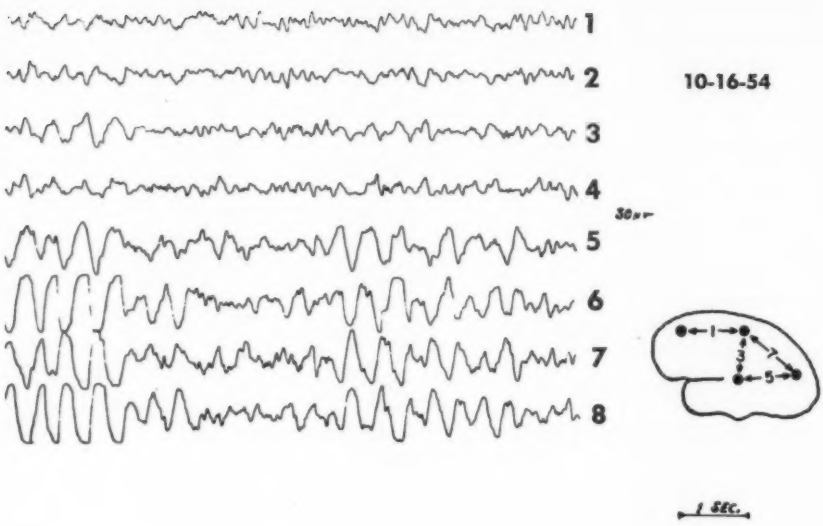


FIG. 1. Petit mal variant pattern appearing synchronously in anterior lead combinations. There was a right anterior cerebral cyst of questionable origin.



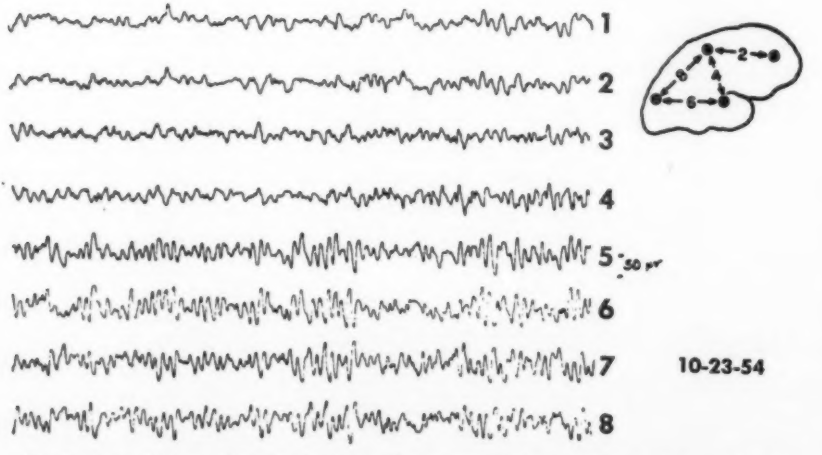


FIG. 2. A severely slow tracing obtained from a 10 year old child with periodic headaches and a migraine family background. The child presented a hemiparesis, hemianopsia, and confusion when recorded (above). Clearing of the clinical picture and of the electroencephalographic tracing correlated well (below).

signs of hemiparesis. The antecedent history may include convulsion but may be so vague otherwise as to leave an open choice between the onset of an encephalitic illness and the existence of a neoplasm. In such instances it is important to know that the postictal manifestations of ordinary childhood seizures are sometimes prolonged. We have observed, for example, high voltage, quite slow activity opposite to a hemiparesis (Todd's paralysis), with both clearing over a few days. Neither does the postictal record provide a reliable estimate of the base of cerebral disorder, out of which a seizure pattern develops periodically. For that purpose tracings obtained in seizure-free intervals give more reliable data.

Migraine in children is attracting more attention than formerly. The diagnostic criteria cannot be as stringent as for the corresponding headache of adults, and we have been content ordinarily to classify as migrainous any severe recurring headache, particularly if precipitated by emotional disturbance or fatigue or when there is a positive family background. An epigastric sensation may occur as a prodrome, or nausea and vomiting may accompany the headache. In some cases a rather unequivocal epigastric prodrome (aura?) is described. If there are proved convulsives in the family, if the headaches are of sudden onset and short duration, and if drowsiness is the usual aftermath, it is perhaps justifiable to regard the cephalgia as a convulsive equivalent. In 285 children with the chief complaint of headache, after excluding a small minority with established brain tumor or other focal process, the author found that 50 per cent of the tracings showed slow deviations from the accepted standards for age. Among those were some in which the pattern suggested that of interseizure activity in child convulsives. Besides such routine headache complaints in children, one sees occasionally severe headache associated with hemiparesis, hemianopsia, and confusion, the symptoms disappearing after an interval of one to several days. Such cases probably belong in the category of familial hemiplegic migraine; in one such case (figure 2) a quite slow tracing was recorded on the day of the headache, with resolution over the ensuing two weeks.

Infants and children with brain tumor usually present pressure signs of headache and vomiting with or without papilledema. The younger an infant the more conservatively should lateralized or focalized patterns be interpreted (figure 3), for the occurrence of a focal pattern in a young child does not necessarily establish the site of the tumor as immediately beneath the electrodes through which it was recorded. Even hindbrain tumors may occasion lateralized disturbance of brain activity in infants. Third ventricle and other midline tumors of children and adults are apt to occasion projected slow activity showing bilateral rhythmicity. If the tumor is located anteriorly in the third ventricle, the frontal combinations are likely to display the pattern; if posteriorly, the occipital leads indicate the disturbance. A third ventricle tumor may also invade the basal region asymmetrically causing spurious lateralization to the more affected side.

Diffuse generalized slowing of the record is the rule in meningitis, although this may be accompanied by more significant slowing or higher amplitude in some areas as compared with others. If the condition is fulminating, as may be

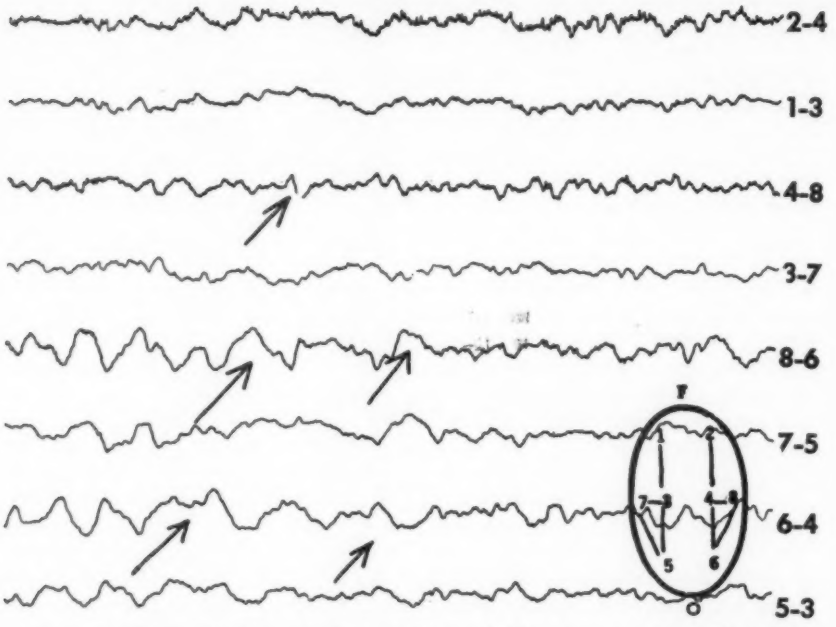


FIG. 3. The reliability of brain tumor localization in infants and children increases with age. This tracing obtained at three and a half years provided an exceptionally good localization. Such is not always the case.

the case with influenzal meningitis for example, electrical activity may be entirely suppressed at the height of the illness. As the child's situation betters slow waves then commence to reappear, with eventual substitution of frequencies approaching the normal in beat pattern. Followed during the months succeeding the acute illness, other focalizing changes may appear out of which a convulsoid pattern develops. With brain abscess the events may be similar, with the possible addition of lateralized or focalized accentuation related to the site of the abscess. Residual slow activity may persist over the site of a resolved abscess.

A diagnosis of encephalitis in childhood is difficult to establish unless there is a causal relation to a preceding infectious disease or vaccination. Otherwise the diagnosis in recovered cases rests upon exclusion alone. In all such instances slowing of the tracing has been the usual feature, the degree being generally proportionate to the clinical estimate of the severity of the illness. Such slowing, however, must be interpreted in the light of the entire clinical picture for, as pointed out by Moyer,[4] an encephalitic process may stimulate respiration giving sustained increase in rate and depth. In two cases of proved subacute encephalitis that we have examined (one reported previously by Landau and Gitt[5]) slowing was also the rule, slow bursts as reported by Cobb and

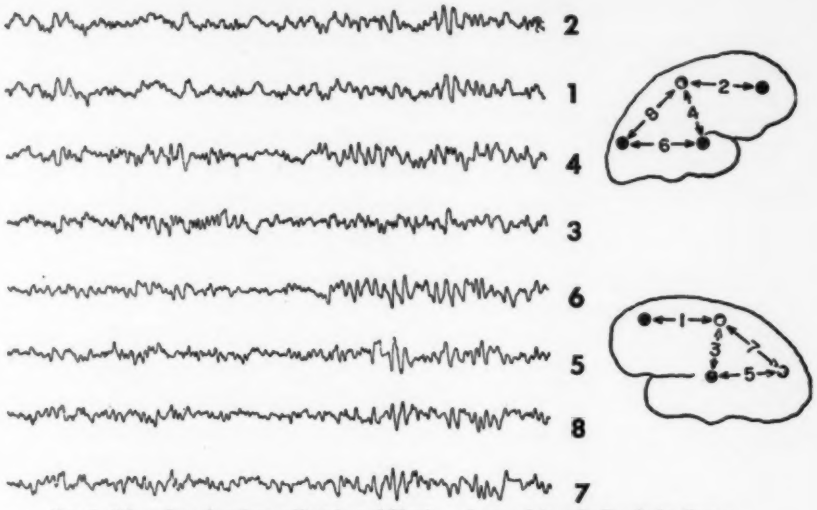


FIG. 4. Minor slow alterations evident in a child wit h proved juvenile Tay-Sachs disease.

Hill[6] being an occasional feature.

The electroencephalographic changes incident to repeated topical applications of Asterol are selected to illustrate how disturbance of brain activity may develop as a neurotoxic manifestation. Forty children scheduled for scalp applications of the agent were given pre-therapy electroencephalograms and followed during treatment.[7] In three cases significant alterations developed during treatment, characterized by a marked slowing which developed within a few days. In all there was a suspicion of finger transfer from scalp to mouth, and the changes disappeared when the applications were discontinued. After the electroencephalograms had returned to normal, applications were started again in two of the children with suitable precautions against finger transfer. Therapy was then completed without further incident.

In the hypoglycemic manifestations of children slower frequencies are also observed. This is not a simple shift in the wave spectrum as the blood sugar level is reduced; rather, discontinuities become evident and the over-all severity of the change appears to correlate rather better with the rapidity than with the extent of the drop in blood sugar concentration. We have studied in detail one instance of hypoglycemia occurring in a child with petit mal attacks. Here intermediate drops in blood sugar increased the frequency of occurrence of 3/sec. spike and wave bursts; on the other hand, marked diminution in blood sugar caused the spike wave bursts to disappear entirely. Thus partial interference with oxidative glycolysis may augment, and marked interference may inhibit altogether the appearance of organized spike-wave bursts.

If hydrocephalus develops slowly it may not occasion significant electroencephalographic alteration, at least until the condition is quite far advanced. Thus

the electroencephalogram is not a particularly useful diagnostic procedure. Similarly, in infantile chronic subdural hematoma findings have been quite variable. Phenylpyruvic oligophrenia, hypocalcemia,[8] and Tay-Sachs disease[9] (figure 4) may produce slow deviations from the normal expectancy for age, the degree of departure from the norm serving as an estimate of the severity of the condition. In cases of tuberous sclerosis with seizures examined in our laboratory convulsoid patterns have predominated.

A diffusely altered electroencephalographic tracing interpreted by itself may be nonspecific, and the greatest usefulness of the test is realized when the results are integrated with the details of history and with the neurologic, roentgenographic, and other pertinent laboratory data. Apart from the detection of convulsive states, the purpose the electroencephalogram serves best is in providing a direct index of the brain's activity, the changing status in serial tracings pointing either to improvement or to deterioration. In all estimates of deteriorating status the protective balances provided by the cerebral homeostatic mechanism must be taken into account. An abrupt deterioration in a tracing suggests that the protective mechanism has given suddenly in response to continuing stress.

PAROXYSMAL DISORDER IN ADULTS

Convulsions, headache, vertigo, and carotid sinus syncope are characteristic of paroxysmal disorder. Certain factors are often overlooked in considering the value of the electroencephalogram in convulsive seizures. Excepting those psychomotor cases in which anterior temporal spikes[10] are uncovered by a sleep tracing, a normal waking interval record suggests a good response to therapy; conversely, the more disordered such a tracing the more difficult anticonvulsant control is apt to be. A subject who has a first seizure between ages 20 and 50 remains a tumor suspect even though the tracing be normal. Unless immediate air study is decided upon, serial tracings should be done since a neoplastic focus may not have matured sufficiently at the time of a first seizure to reveal a focal process in an electroencephalogram taken a few days later. Following a first seizure in an adult any definite focal pattern, however minor and whether or not it becomes more clear in successive tracings, is suspicious of underlying neoplasm, and particularly so if seizures become more frequent, intense, or difficult to control. After the age of 50 there is an increasing incidence of electroencephalographic disorder due to hypertension or arteriosclerosis. Even so the possibility of tumor should be entertained in the case of clear focalized disorder accompanying a first seizure occurring in an adult at any age.

In an electroencephalographic study of 1,000 cases of periodic headache from which the obviously organic causes had been excluded, Ulett, Evans, and O'Leary[11] showed that fast or slow disorder or some mixture of the two occurred in a significant proportion of such tracings (15.8 per cent). Focal records were rare. The percentage of clearly disordered records was significantly higher among the females of the series, and in both sexes fast disorder led the slow in incidence by four to one. The ratio indicates that a clearly slow record associated with the symptom of headache can be weighed as having more organic significance than can a clearly fast one. A small percentage of tracings in such

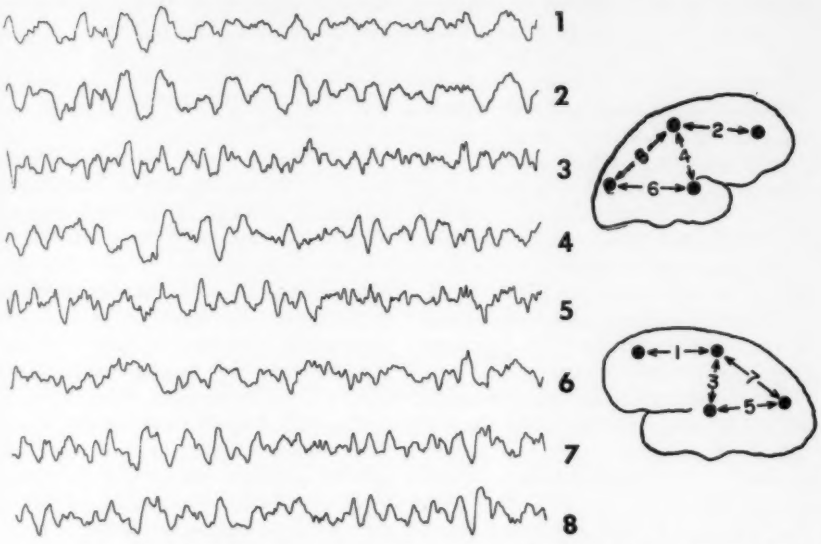


FIG. 5. Right frontal (channel 2) dominance of slow pattern in an 82 year old man later proved to have a right frontal glioblastoma.

headache cases show an "interseizure type of convulsive pattern" manifested by pace irregularity, relatively high voltage, and hypersynchrony. It is in such instances, if any, that a periodic headache may improve under anticonvulsant medication.

A headache caused by brain tumor occasionally masquerades as one of migrainous type. For that reason the finding of a definite focalized or lateralized pattern, however minor, that repeats from one tracing to another, calls for a follow-up and air study if the headache worsens. An experienced clinician is usually able to detect those headaches suspicious of organic causation; electroencephalography is a definite aid in all cases of protracted headache.

In true vertigo considered as a paroxysmal complaint the value of the electroencephalogram is difficult to estimate, particularly if one considers the significantly higher incidence of vertigo in the later decades when the incidence of disordered tracings is also increasing. When the cause of vertigo lies in hydrops of the labyrinth, in the brainstem, or in angle pathology, the electroencephalogram cannot be said to provide useful data. However, when vertigo is occasioned by a focal cortical disturbance (as of a lip of the Sylvian fissure), the electroencephalogram may provide significant information. There are also cases of vertigo which are migraine or convulsive equivalents, and the latter may respond to anticonvulsant medication. Here also the crux of the problem lies in the neurologist's ability to separate a relatively few cases of structurally based vertigo from the many others in

which the cause is difficult to ascertain.

Carotid sinus attacks may in part simulate convulsive ones, and the electroencephalogram is a useful diagnostic procedure when combined with electrocardiogram and carotid sinus massage during recording. Often enough older patients with cerebral symptomatology suggestive of carotid occlusive disease will show carotid sinus sensitivity. These cases should not be relegated to the category of carotid sinus syncope too quickly. Where the classic syndrome appears in younger patients we have sometimes been able to demonstrate a clear association between carotid sinus massage, cardiac slowing, and the appearance of lateralized slow waves over the territory of supply of the carotid whose sinus is being stimulated. Usually the slow waves appear in the electroencephalogram some 6 to 10 seconds after pulse slowing commences, and may be accompanied by symptoms referred to the opposite side of the body.

Momentary reduction in consciousness in elderly patients, or even syncopal attacks, may be difficult to distinguish from minor seizures or even full convulsive episodes. Such instances belong in the category of Adams-Stokes attacks, and ordinarily we have been unable to show significant findings in the interval tracings apart from disorder otherwise attributable to arteriosclerosis or to reduced cardiac functioning. However, an electroencephalogram is taken in the sitting or reclining position, and the attacks are more likely to appear when the person is standing or walking.

Electroencephalographic alterations in individuals with narcoleptic and cataleptic attacks are most often of minor import and nonspecific. Occasionally the resting frequency of the waking record is mildly slow; again rapidly developing and terminating sleep sequences may be scattered through the tracing.

TUMOR, SUBDURAL HEMATOMA, AND ANEURYSM

In forebrain tumor one can be fairly confident of establishing a lateralizing or localizing diagnosis in the mildly to moderately obtunded patient where neurosurgical intervention is an imminent consideration. It may even be possible to estimate the level of intracranial pressure roughly by the amount of diffuse slowing upon which the localized pattern is superimposed. Flattening of the tracing obtained from lead combinations opposite to the side of the focal pattern suggests ventricular shift, and if the major slow disturbance centers at a temporal electrode and opposite-sided suppression is marked, we believe that there is a good chance of herniation of the uncus through the incisura with sudden worsening of the patient's condition. Accordingly such a situation is reported immediately, for the case bears careful watching with the view of expediting surgery.

The electroencephalogram does not distinguish between primary and metastatic neoplasm, although the finding of more than one focus may suggest the latter. Even a small metastatic tumor can be surrounded by a large area of marked edema, and then the region of scalp-registered disturbance is likely to be quite large by comparison with the size of the tumor. The electroencephalogram is not reliable for differentiating between a focus due to encephalomalacia and one due to neoplasm, and this is particularly true when cerebral arteriosclerosis is in question and several subclinical strokes might have preceded

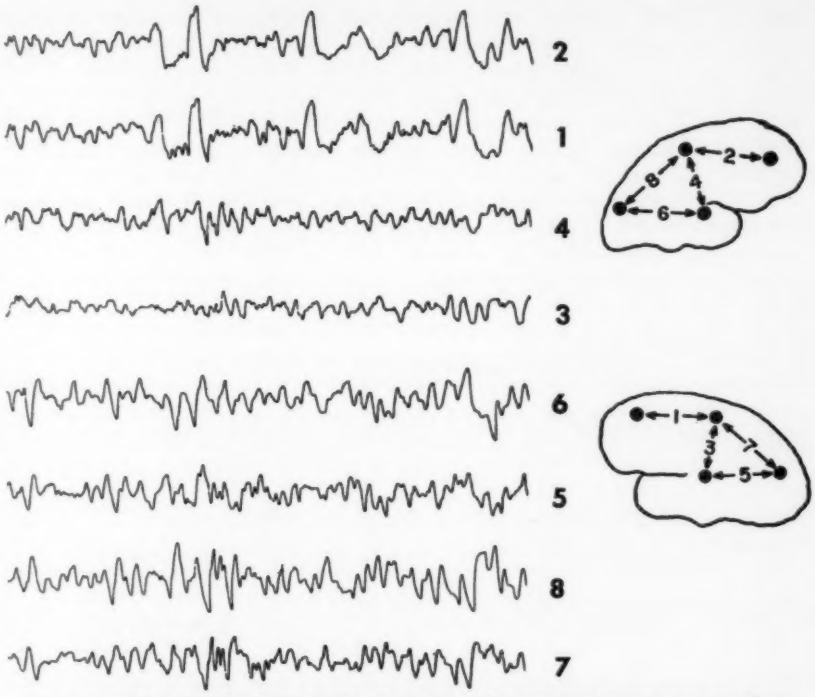


FIG. 6. Anterior third ventricle tumor (adult). Note bifrontal slow transients appearing synchronously in the frontal combinations (channels 1 and 2). Such interpretation only has value as a part of the entire assay of the patient, for similar transients might appear in convulsive disorder.

the appearing of symptoms leading to the present examination. However, the electroencephalogram does give useful localizing information, and one can depend upon other indices, such as a fluctuating state of consciousness, to weigh the evidence in favor of a space-consuming process. Figure 5 illustrates the electroencephalogram in one such problem case, an 82 year old male without papilledema who came to ventriculography and removal of a right frontal glioblastoma.

When personality deterioration has proceeded slowly over a period of months in an older person and neurologic lateralizing signs are obscure, the problem of deciding between frontal neoplasm and presenile dementia may arise. Diffusely represented slow disorder without lateralizing or localizing tendencies points away from tumor and toward an aging process. Third ventricle and other deep-lying midline forebrain tumors present difficulties, however.

Bilateral synchronous disturbance of pattern is the only significant electroencephalographic indicator of a deep-lying midline space-consuming process, and the interpretation is based upon experience derived from the correlation of the electroencephalogram with surgical or

pathologic data in other such cases. Synchronous bifrontal slow processes coupled with less evident disorder elsewhere in a tracing is suspicious of an anterior midline lesion. Deep-lying frontal gliomas can give rise to 1 or 2/sec. bifrontal synchronous waves, occurring with fair continuity or in clusters. However, both bromism and electrolyte imbalance can occasion a similar picture, so any electroencephalographic interpretation must be made after these other possibilities have been ruled out. Anterior third ventricle tumors sometimes show high voltage 3 to 6/sec. sequences, also bilaterally synchronous (figure 6). Posterior third ventricle and quadrigeminal plate invasive processes can occasion high voltage 3 to 6/sec. occipital activity (figure 7). As indicated previously the same generalizations also hold in children, but with the reservation that children with convulsions far exceed in number those with tumor, and among convulsive patients paroxysmal disorders may be chiefly evident in either frontal or occipital combinations.

Among the most difficult tumor diagnoses are those few in which growth is slow and goes undetected in one or several air studies; yet such a patient may show slowly progressive symptomatology. If, for example, the alarm symptom is the occurrence of jacksonian seizures

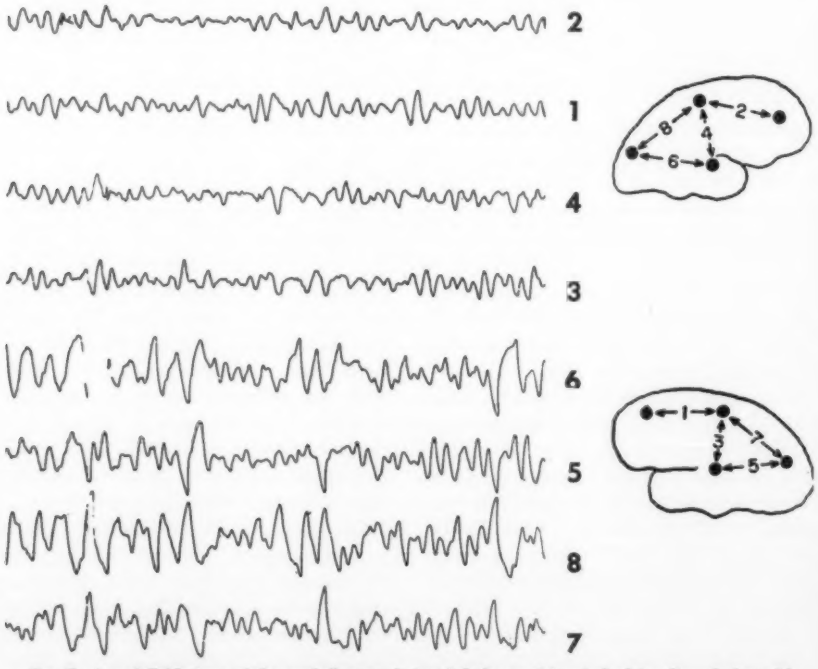


FIG. 7. A medulloblastoma of the cerebellar vermis invaded the quadrigeminal plate. Record shows bioccipital slow activity, more marked on the right (channels 6 and 8).

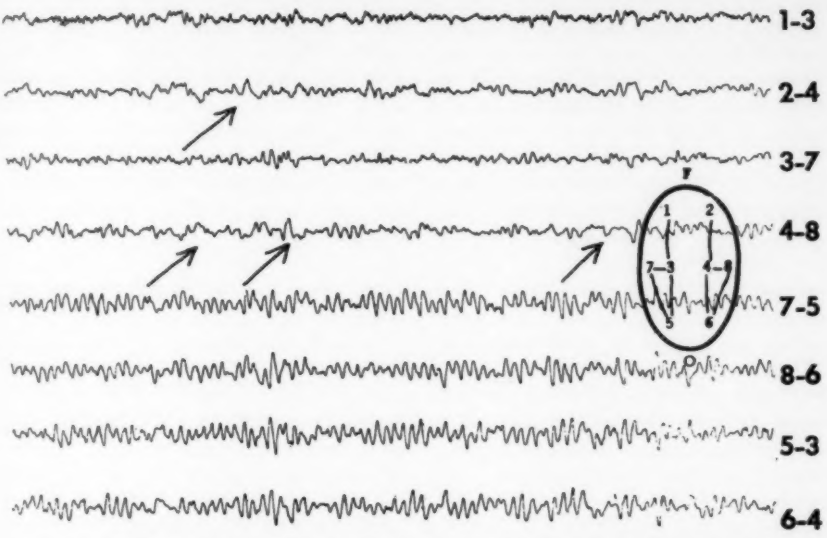


FIG. 8. Illustrates the need for careful follow-up on all minor focal transients that repeat from one tracing to another. Particularly in tumor suspects carried upon an outpatient basis, such minor lateralizing differences bear careful watching.

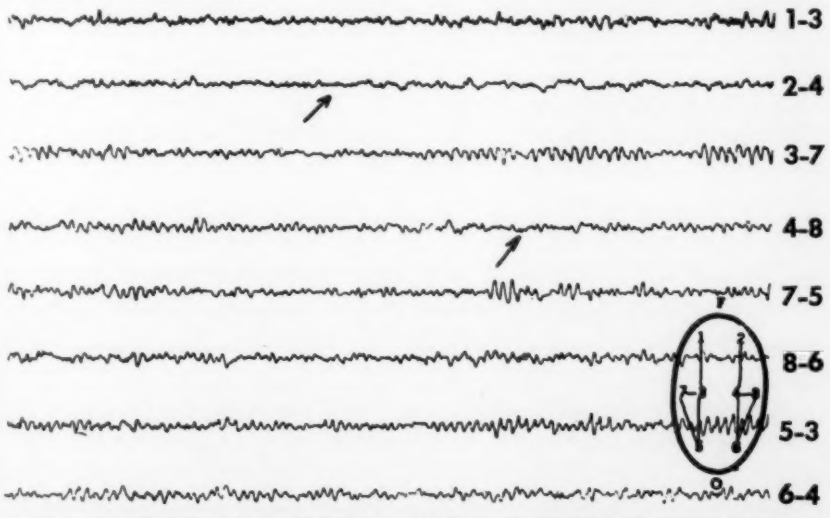


FIG. 9. A subdural hematoma was proved later in this patient recorded first upon an outpatient basis. Note that the tracing is relatively well ordered except for the right anterior triangle suppression. Decompensation can occur rapidly with sudden worsening in the state of the patient and the appearance of slow activity of high voltage in the tracing. The record may then simulate that often seen in forebrain neoplastic processes.

confined to a hand and later the seizure pattern becomes more generalized and severe and recurs more frequently despite anticonvulsant medication, the suspicion of tumor must remain and may lead eventually to exploration of the suspected site. We have seen such cases in which a very minor electroencephalographic focus has been present from the beginning (figure 8) and has not increased in prominence. More often, however, such a focus increases in prominence and in area of distribution; thus all such cases should have serial study to detect electroencephalographic evidence of progressive neurologic deficit.

In proved cases of hypertensive intracranial hydrops ("pseudo-tumor") the electroencephalogram may be entirely normal.

Chronic subdural hematoma requires little additional discussion. What is known of the mechanism of its growth suggests that for a time cerebral homeostatic mechanisms may succeed in masking the increase in size of this space-consuming process insofar as electroencephalographic localization is concerned; thus a single recording might provide minor, if any, changes to indicate the location (figure 9). However, decompensation can occur rapidly, and within one or a few days a clear-cut slow wave focus appears over the site. This suggests that the electroencephalographic problems encountered in outpatient ambulatory and in hospitalized, partially obtunded patients may differ markedly, the latter sometimes providing an easy localization, the former a minor one or none.

Millar[12] has recently reported upon the use of the electroencephalogram in cases of subarachnoid hemorrhage. A cerebral aneurysm that is subject to surgical treatment ordinarily lies in or close to the circle of Willis and remote from the electrode distributions of routine recording. Thus it would be unlikely for an unruptured aneurysm to be detected by electroencephalography, and we have recorded normal tracings when there is a radiologically discernible large calcified aneurysm of the base. However, one that is leaking or has bled presents somewhat better prospects for localization, the inferences to be made being based upon past efforts to correlate electroen-

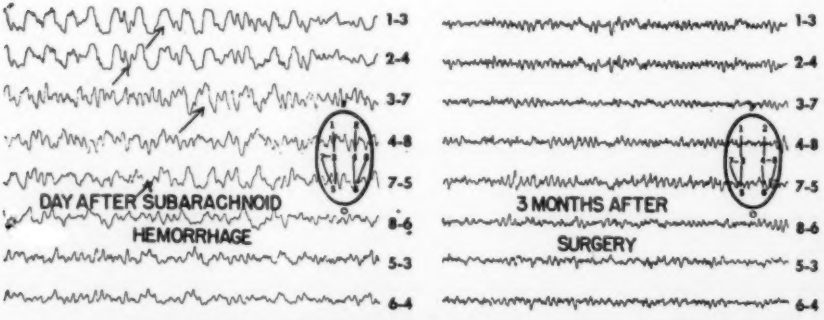


FIG. 10. A distribution of slow activity that may occur in the case of subarachnoid hemorrhage due to ruptured anterior cerebral aneurysm. Compare with figure 14, a proved case of electrolyte imbalance. The most effective neurologic use of the electroencephalogram is made when the tracing is consided as one phase of the total examination of the patient.

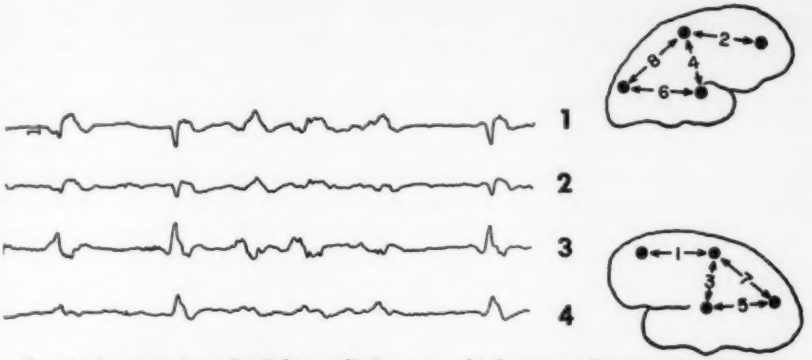


FIG. 11. A suppressed record with low amplitude paroxysmal spike processes from a case of cryptococcus meningitis associated with Hodgkin's disease.

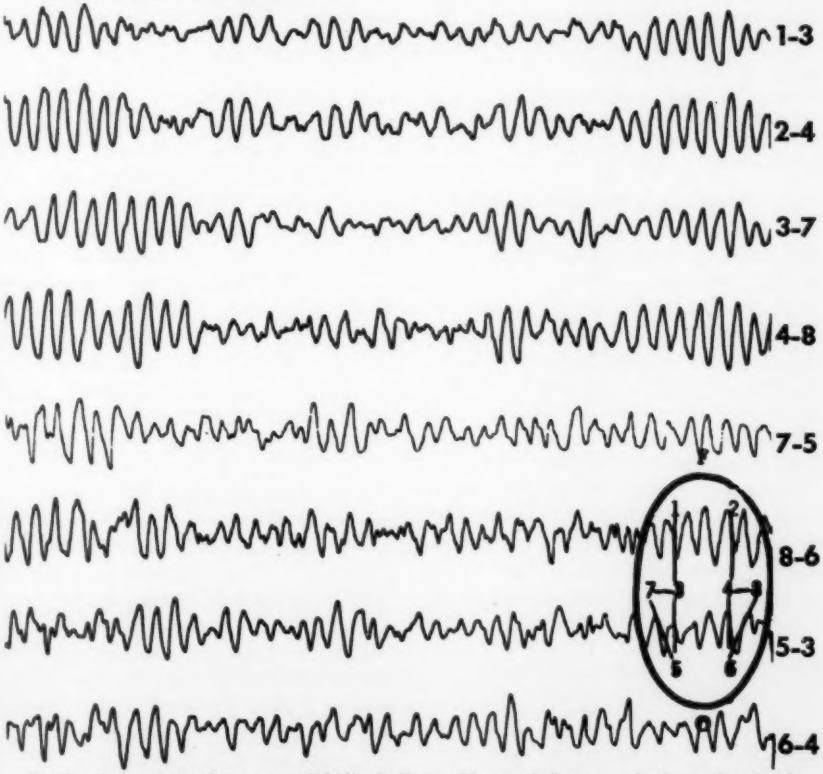


FIG. 12. A slow tracing from a case of Addison's disease. The record change may be due to the adrenal insufficiency itself or a result of the associated electrolyte imbalance.

cephalographic with surgical and pathologic data. Given a history of subarachnoid bleeding and an electroencephalographic tracing which shows anteriorly distributed slow activity, perhaps more prominent in one or the other frontal lead (figure 10), the inference is permissible that an aneurysm will be found in the anterior cerebral system. Aneurysm near the bifurcation of an internal carotid may provide a lateralized slow disturbance over the central region; perhaps this is attributable to obstruction in the middle cerebral circulation. In view of the advances that have been made in angiography, the electroencephalogram can only be said to provide preliminary data; however, in some instances such information may be of considerable value to the neurosurgeon.

MENINGITIS IN ADULTS

Rarely does a single tracing provide useful diagnostic information in meningitis, and then only if assessed in the light of the total examination of the patient. Besides slowing and even generalized suppression of activity in fulminating cases, bizarre-appearing slow spikes of low amplitude can occur. A case of cryptococcus meningitis complicating Hodgkin's disease is selected for illustration (figure 11). Rather than as a diagnostic procedure, the electroencephalogram may find its principal usefulness in meningitis as a bedside procedure, brief tracings taken several times a day being used to assay improvement or deterioration in the patient's status.

ENDOCRINE, METABOLIC, AND ELECTROLYTE DISTURBANCES IN ADULTS

When marked hypothyroidism exists some slowing of the electroencephalogram is to be expected. The intermediate slow frequencies sometimes recorded in cases of myotonic dystrophy are perhaps attributable to associated hypothyroidism. Hyperthyroidism may increase the frequency of the waking electroencephalogram, and in a series of cases of marked thyrotoxicosis studied by Becka, Condon, and Gibbs[13] even clusters of high amplitude fast spikes were reported. Hypocalcemia can cause slow changes. In Addison's disease (figure 12) a shift toward the slower frequencies may appear, for which one of several factors may be responsible, among them the rapid rate of sodium excretion and the deficit in extracellular body fluid.

Diabetics of long standing, especially those in which the condition is associated with hypertension, may show fast and slow patterns as evidence of mild to moderate disorder; occasionally focal trends develop which relate to transient symptoms referred to the opposite half of the body. We have seen such cases in which the focal trends disappeared during treatment. With porphyria (figure 13) either a slow shift in frequency or hypersynchrony and pace irregularity may occur. Adams and Foley[14] state that as patients pass into liver coma paroxysmal slow sequences first appear at a frequency of 1½ to 3/sec.; as the stage of coma is reached the record may become continuously that slow. Very slow activity also characterizes diabetic and uremic comas so that a coma record incident to a metabolic disturbance does not seem to be specific in itself, even though the record changes during the approach to coma may be significant. Walton, Keloh, Osselton, and Farrall[15] have also shown that abnormal slow activity may occur in pernicious anemia.

Electrolyte imbalance uncomplicated

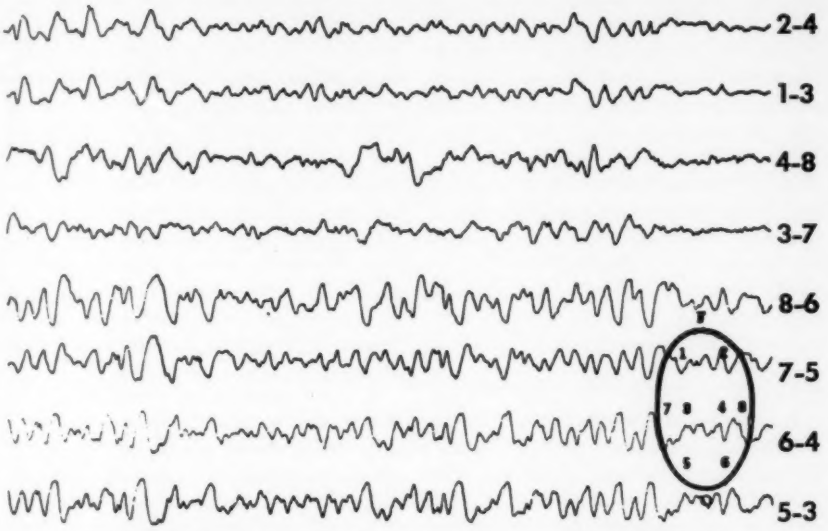


FIG. 13. Porphyria may be associated with slow alterations in the electroencephalogram.

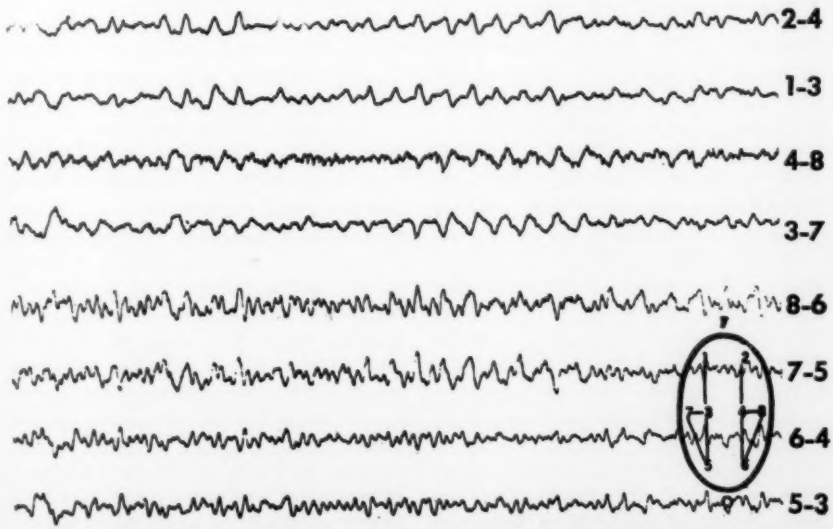


FIG. 14. Tracing from a proved case of electrolyte imbalance. When the imbalance was corrected the tracing returned to normal.

by other disorder can produce reversible slow alterations in the electroencephalogram, and if the electroencephalographer fails to consider this possible source of error he may erroneously ascribe the changes to a structurally based disorder. Figure 14 illustrates a disordered tracing obtained subsequent to repeated vomiting. When electrolyte equilibrium was restored the alteration disappeared. Compare the tracing with figure 10 (left) obtained following a subarachnoid hemorrhage due to rupture of an anterior cerebral aneurysm.

ELECTROENCEPHALOGRAPHY IN AGING

A brain wave tracing obtained during healthy aging is ocasionally as normal as one from a younger adult, but with the marked rise in incidence of both vascular and metabolic debility during the senium, it is understandable that a significant amount of electroencephalographic disorder may occur even among neurologically asymptomatic individuals. Thus the number of records that should be called "borderline" or "indeterminate" must be increased appreciably if we are to expect electroencephalographic disorder to correlate well with neurologic and psychiatric estimates of the aged individual. As always, a focal disorder, particularly one which fits the expectancy from the neurologic history and findings, has much more significance than a diffuse one.

In considering the effects of vascular debility upon the electroencephalographic tracing there are other considerations of importance besides the cerebral arterial system itself. Carotid occlusive disease and defective cardiac output may gradually deplete the available energy reserves of the brain so that a relatively minor focal insult can produce irreversible damage. We also see patients who show frequently recurring, transient lateralizing symptoms, such as relatively brief aphasic episodes or numbness and tingling on one side of the body. Such cases present the problem of a threatened stroke, and an electroencephalographic focus over the presumed site of the disturbance is an expected finding. In other patients examined for senile mental changes attributable to marked arteriosclerosis, multiple slow foci may be superimposed upon a base of irregular frequency slow activity.

A rare coincidence is considered in detail here because it illustrates that a slow focal disorder can appear in an electroencephalogram preceding the evidently related stroke (figure 15). A 64 year old hypertensive female patient who had no history of an earlier stroke was given a routine electroencephalogram at 3 p.m. The tracing was not unusual except for a right frontal slow focus, the waves appearing in bursts having a duration of 2 to 3 seconds each. At the time she was neurologically asymptomatic, except for a nonlocalized headache from which she had suffered over the preceding six months. At 6 p.m. she developed a left hemiparesis of sudden onset, presumably due to cerebral thrombosis, since spinal fluid findings were noncontributory. The hemiparesis improved and the electroencephalographic focus had disappeared three weeks later. This case illustrates that the conditions leading to an occlusion can be manifest for a time before the clinical signs of stroke appear, and that a focal pattern will sometimes disappear entirely even though lateralized neurologic deficit remains. In other instances we have followed slow wave foci of pre-

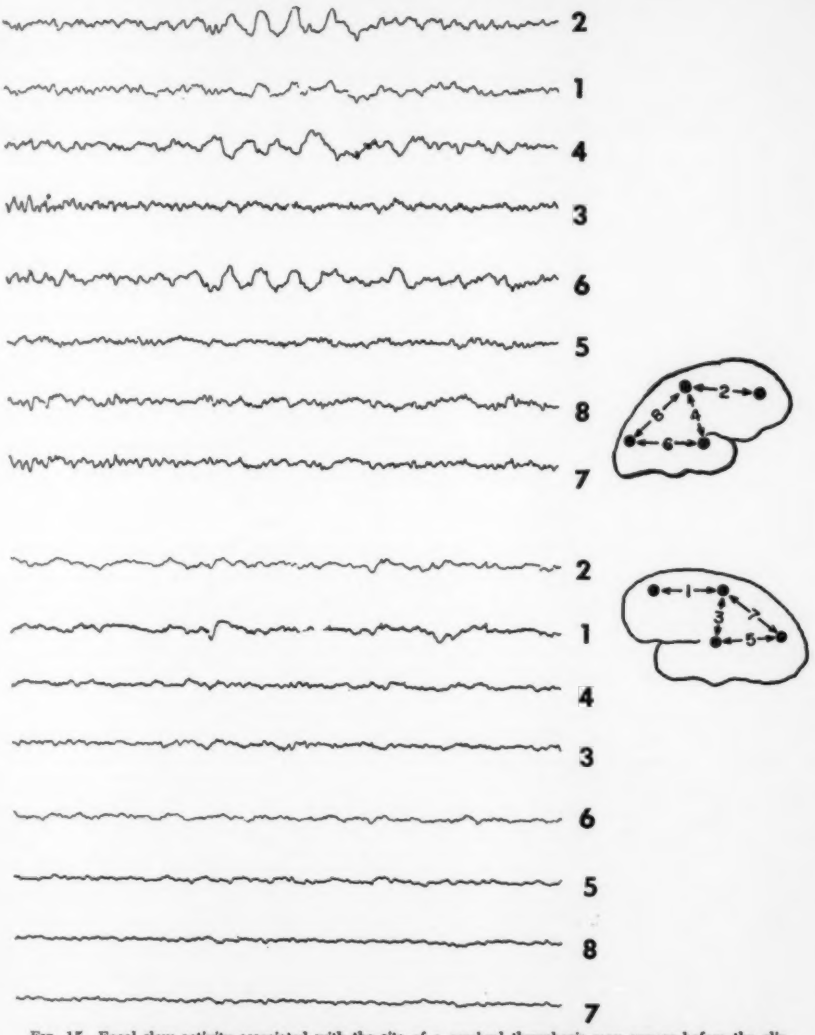


FIG. 15. Focal slow activity associated with the site of a cerebral thrombosis may appear before the clinical manifestations of the stroke. Record upon a hospitalized patient obtained three hours preceding a clinical stroke. Note episodic slow activity in leads 2, 4, and 6.

sumed vascular etiology which persisted for years following an occlusive episode.

CONCLUSIONS

Electroencephalography which concerns itself exclusively with seizures and localizing diagnoses cannot fully exploit the manifold neurologic uses of the technic. The clinical neurologist should view

the method from the broader perspective of an adjunct to the neurologic examination. If the interpreter has the experience to integrate electroencephalographic findings with history, examination, and other laboratory data, the procedure can make a valuable contribution both in diagnosis and in gauging improvement during treatment.

Where this is realized the electroencephalogram is used increasingly by neurologists and internists alike in evaluating the cause of a symptom or group of symptoms pointing toward a forebrain lesion. Certain symptoms can manifest either primary central nervous system involvement or a systemic disorder. A case in point is the confusion, sleepiness, apathy, and even disorientation that may accompany electrolyte imbalance or bromism. It would be a serious error to overlook such systemic possibilities in interpreting bilateral slow sequences in an electroencephalogram. If overlooked, diagnostic judgment can be weighed in the direction of an irreversible forebrain organic change, whereas in fact the causative imbalance is systemically derived and readily correctible.

In considering space-consuming processes the conviction that a history of progressive neurologic deficit exists is more important in reaching an eventually correct diagnosis than is localization or lack of localization in a first electroencephalogram. Successes in localizing brain tumors in hospitalized cases where neurosurgical intervention is imminent can lead to misplaced confidence in normal-appearing records obtained in some outpatient cases. A minor focal pattern is sometimes seen in retrospect to be an early sign of tumor, and given a history of progressive deficit, serial recordings should be done whether or not an air study has been negative. Nor can it be said unequivocally that clearly paroxysmal focal patterns do not occur with space-consuming processes, for occasionally we have seen the site of one signaled by either a slow spike or a spike and wave.

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Amyloid Polyneuropathy

John F. Sullivan, M.D., Thomas E. Twitchell, M.D., Gherardo J. Gherardi, M.D. and Willard P. VanderLaan, Jr., M.D.

A CONSTANTLY RECURRING PROBLEM in clinical neurology is the large group of polyneuropathies which defies etiologic classification. We believe that it is possible to identify and thus to separate from this group those patients presenting with neuropathy due to primary amyloidosis. This is a disease which affects many organs, and it is this feature of a chronic neuropathy occurring in a patient who shows evidence of disease in other systems which will enable one to identify the disease process. Each of the cases described below presented with a chronic sensorimotor neuropathy, hoarseness, and electrocardiographic changes, a combination of symptoms and signs which suggests primary amyloidosis. A review of the literature indicates the frequency of involvement of the heart and larynx in this disease. It is evident, therefore, that a considerable proportion of patients with primary amyloid neuropathy will present with evidence of involvement of these organs.

CASE REPORTS

Case 1.—A 50 year old man was examined on April 2, 1951. Ten years earlier he had weighed 226 lb. but thereafter he lost weight gradually until at the time of examination he weighed 146 lb. Five years previously he had had an episode of weakness, sweating, and nausea presumed to be due to heart disease; he was placed on digitalis which he took in the intervening years. For two and a half years he had been aware of swelling of his ankles on dependency. At that time he began to note the development of weakness and fatigue of his legs, with tenderness of the feet and calves. For one year he complained of numbness and tingling starting in the feet and extending to the knees. A few months prior to examination he began to note weakness of his hands but no sensory change. His voice had also changed and he had become quite hoarse.

On examination he was alert, cheerful, and showed no evidence of dementia. His skin was of a fine texture and of an odd color, not exactly pale but with a slight yellow tinge. His voice was husky with a very narrow range of tone, and examination of his vocal cords showed thickening and a slight amber discoloration. The cranial nerves were normal otherwise. His blood pressure was 126/96, and his heart was enlarged to percussion with a rate of 94. The liver and spleen were not palpable. Examination of the motor system showed thin musculature, but that about the shoulder and upper arms was quite powerful. There was moderate weakness of both hands. He had minimal triceps reflexes, but all other tendon reflexes were absent. Abdominal reflexes were active. In the lower extremities weakness was quite profound at the ankles, and there was some weakness of the thighs but less marked than in the periphery. The patient had tenderness on palpation

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of the muscles of the feet. There was a sensory loss beginning at the knees, becoming more severe toward the feet. Pain sensation was absent from the mid-shin; touch was absent in the feet. Vibratory sensibility was absent to the knees, and position sense was grossly defective at toes and ankles. Minimal sensory loss was also present in the hands, with touch slightly impaired in the fingers. The peripheral nerves were not enlarged to palpation.

Laboratory studies revealed normal urine and blood chemistries. He had a mild macrocytic anemia, and the blood sedimentation rate was slightly elevated to 20 mm./hr. Bromsulphalein test showed 12 per cent retention at the end of 45 minutes, cephalin flocculation test was 4 plus, and the prothrombin time was 57 per cent of normal activity. The congo red test at the end of 60 minutes showed 75 per cent retention of the dye in the serum. The spinal fluid protein was elevated to 80 mg. Blood and spinal fluid serology tests were negative. Electrocardiogram on admission showed an abnormal tracing with an unusual arrhythmia which seemed to consist in periodic prolongation of the PR interval with Wenckebach's periods and occasional dropped beats. A second electrocardiogram showed auricular fibrillation with many ventricular premature beats. Fluoroscopy showed generalized enlargement of the heart.

Biopsies of skin, cutaneous nerve, and striated muscle showed amyloidosis of all three tissues, with deposition of the amorphous material in diagnostic amounts. The expected staining characteristics were easily demonstrated with congo red stains. In all three locations the amyloid displayed the usual predilection for vessel walls and perivascular areas, with small deposits indiscriminately distributed in the interstitium.

The nerves contained very small and presumably early deposits frequently in relation to the wall of the nutrient vessels mostly of arteriolar or precapillary size (figure 1). The smallest of these had no particular shape and were subendothelial or intramural. In some instances the entire circumference of the vessel wall was replaced by the amyloid with resultant obvious narrowing of the lumen, occasionally to an occlusive degree. The larger deposits tended to be globular and displaced the nerve fibers. The latter appeared to part proximally to each lesion; they were moderately to markedly compressed at the equatorial level of the infiltrate and reunited beyond. Bodian stains for axons failed to demonstrate any definite interruption of continuity, but some degeneration and loss of myelin was indicated with routine stains, although myelin stains could not be done.

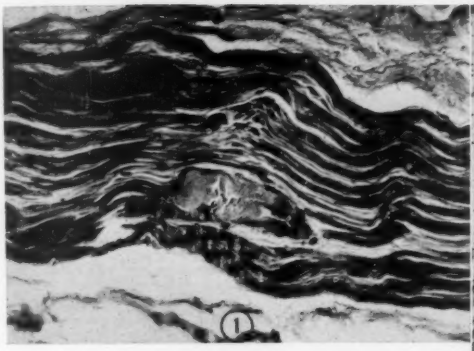
The alteration of striated muscle was considerably severe, being marked by atrophy of entire bundles coupled with atrophy and disappearance of individual fibers. These changes were associated with a condensation and proliferation of endomysial cells and sarcolemmal nuclei. Amyloid deposits were scattered throughout in vessels and interstitium and in small chunks between muscle fibers.

The skin showed amyloid as bundles and amorphous masses replacing or displacing dermal collagen, small arterial walls, and fat cells (figure 2).

Once the diagnosis was established, a course of ACTH was given over a two-week period without improvement. The patient was discharged to the care of his physician. His condition gradually deteriorated, and he expired at home on May 20, 1953.

Case 2.—A 54 year old married woman noted the insidious onset of her present illness one and a half years before examination on August 13, 1951. She first noted a sensory disturbance in the left foot, and then six months later in the right foot; the hands became involved about one year after the onset, again first the left and then the right. Her complaints were predominantly sensory but there was also weakness. Her legs felt quite numb, and there was a continuous ache in the calves. There was numbness and tingling of the soles of the feet and toes. Tingling was also present in her hands, and the patient disliked to touch any cold or hot object because of resultant disagreeable pain. For this reason she wore cotton gloves most of the time. Weakness was marked peripherally, with instability of the ankles and toe-drop. She had also noted that she dropped objects because of weakness of her hands. During her illness she lost about 10 lb. in weight. In addition, for six months before hospitalization, she noted hoarseness which became more pronounced when she talked for a length of time.

Examination showed a well-developed woman who had evidence of chronic weight loss. There was no evidence of intellectual deficit. Her pupils were equal, round, and regular, and reacted normally to light and accommodation.



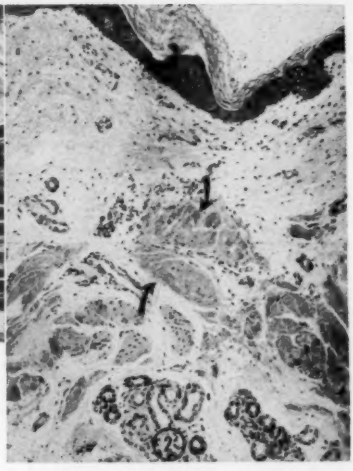


FIG. 1. *Case I.* Biopsy showing longitudinal section of nerve containing perivascular deposition of amyloid. Verhoeff's stain.
FIG. 2. Section of skin showing amyloid deposits in middermis. Congo red stain.

Her voice was hoarse with a narrow range. The tongue was of normal size. The heart appeared normal on examination, and blood pressure was 130/70. The liver was two fingerbreadths below the costal margin, and the spleen was not enlarged. There was diffuse muscle tenderness. Her hands were weak, both in extension of the fingers and in flexion, with slightly increased hollowing of the dorsal interosseous spaces. Weakness was more marked in the legs, particularly the dorsiflexors of feet and toes, but also extended to involve the thigh muscles, especially on the left. There was slight flattening of the anterior tibial muscle group and of the peroneal muscles on the left, but subcutaneous fat made the degree of atrophy hard to determine. Reflexes obtained in the arms were less active on the left than right; they were absent in the legs. The response to plantar stimulation was flexion. Sensory impairment was not complete but was more pronounced in the feet extending to above the ankles. In the hands pain and touch sensations were diminished in the fingers, extending to the wrists on the ulnar side of the hands. Vibratory and position sensibilities were reduced in the right foot and absent in the left. Romberg test was positive. There was a moderate degree of atrophy of the skin of the dorsum of both feet and atrophic changes in the toenails.

Laboratory studies of blood and urine were normal, and two urine specimens were negatice for porphyrins. Blood sedimentation rate was 20 mm. per hour. Glucose tolerance test was within a normal range. Spinal fluid examination revealed no cells and a protein value of 38 mg. per cent. Blood and spinal fluid serologies were negative. Roentgenograms revealed moderate fibrotic changes in the upper lobes of the lungs bilaterally. The heart shadow was small, and the electrocardiogram showed sinus tachycardia, rate 104; PR interval 0.12; QRS 0.06; QT normal; Q present in AVL; T inverted in AVL. The conclusion was that it was an abnormal electrocardiogram.

Biopsies of skin, nerve, and striated muscles were taken and reported to show no trace of amyloid. A subsequent preparation showed a single minute deposit of amyloid (congo red positive) within the perineural covering of the nerve, which was otherwise free of discernible disease (figure 3). The striated muscle specimen contained a few fasciculi in which an appreciable number of individual fibers showed varying degrees of atrophy and minimal degenerative change. Most of the bundles were spared, and no trace of amyloid was found. The skin was within normal limits.

Following discharge from this hospital, the patient was admitted to another hospital and received a course of treatment with BAL without effect. Her disease followed a relentlessly

progressive course over the next 18 months. She was confined to bed during the last year of her life with paralysis of both legs and hands. Her final hospital admission was on June 7, 1953. She had gradually become dyspneic and developed peripheral edema, ascites, and pleural effusion. Her course in the hospital was gradually and progressively downhill, and she expired on June 21, 1953.

Alerted by the first case, we were strongly suspicious when this patient presented with a chronic neuropathy, hoarseness, and minimal electrocardiographic changes, and a clinical diagnosis of amyloid neuropathy was made despite negative biopsies.

Autopsy report: The cardinal pathologic change was disclosed by microscopic examination. This change took the form of a diffuse deposition of a homogeneous eosinophilic, amorphous material which stained metachromatically with congo red and crystal violet with little or no staining variability and was identical to a positive amyloid control. This substance was characteristically deposited in spotty fashion along blood vessels, interstitially within their walls displacing and replacing cells and tissues, spilling over into adjacent structures, and producing varying degrees of concentric narrowing to the point of occlusion. This was particularly evident in smaller arteries and capillary vessels. The amorphous material was dispersed throughout the body's supporting tissues conspicuously sparing the parenchyma of liver, spleen, adrenals, kidneys, myocardium, and pancreas where it was limited essentially to vessel walls.

Amyloid deposition was striking and advanced within and about autonomic ganglia and peripheral nerves of all sizes. Amorphous globular or irregularly-shaped collections within the bundles appeared to affect small nutrient vessels narrowing their lumina, sometimes obliterating them, and to spread therefrom interstitially, mainly displacing and compressing, but also interrupting axons with concomitant degeneration and demyelination. Smaller nerve bundles, in addition, were completely encased in this smooth substance (figures 4 and 5).

The heart weighed 290 gm.; the muscle was flabby, and both ventricles were dilated. The only traces of amyloid were a few foci in the pericardial fat and a conspicuous coronary artery involvement with spread to surrounding fibrofatty tissue and compact engulfment of accompanying nerve bundles (figure 6). The coronary arteries were also the seat of a mild nonocclusive arteriosclerotic process. The myocardium was edematous and showed a fairly diffuse infiltration of the interstitium with polymorphonuclear leukocytes and small and large mononuclear cells. Fragmentation of fibers was diffuse. The valves were free of disease. Many lymph nodes were enlarged and almost totally replaced by massive amyloid deposits which completely replaced the fibrous framework, overran the stroma distorting the architecture, and overflowed into the surrounding fat obscuring their outlines. This was the only location where the character and compactness of the deposit was of such a degree as to engender more than a mild histiocytic reaction to the extent of a foreign-body giant cell proliferation. Minimal deposition was present in striated muscle.

Diagnosis: Primary amyloidosis involving mainly blood vessels, lymph nodes, and peripheral nerves (including pericardial nerves). Interstitial myocarditis, acute, diffuse. Evidence of cardiac failure: cardiac dilatation, bilateral hydrothorax, congestion of lungs and liver.

Case 3.—A 59 year old man was admitted to the hospital on August 2, 1953. One year before entry he became aware of an aching pain in the left great toe and noted a tightness and hypersensitivity across the sole. Then numbness developed in the foot and calf. About six months later tightness and numbness developed in the right foot. A month later numbness appeared in the fingers. Weakness of the legs, unsteadiness of gait, increasing numbness and clumsiness of the hands gradually developed. About six months before hospitalization he noted that his face had become quite thin although his body elsewhere remained well nourished. His voice had been hoarse for many years.

On examination the patient showed a remarkable degree of atrophy of the subcutaneous tissue of the face with loss of the fat pads of the cheeks. His voice was quite hoarse, and examination revealed laryngeal polyps. General physical examination, other than the neurologic, showed his liver to be enlarged to four fingerbreadths below the costal margin. Clubbing of his fingers was present, but no abnormalities of heart or lungs were noted. Blood pressure was 130/80. Moderate pitting edema of the feet and ankles was present. He had

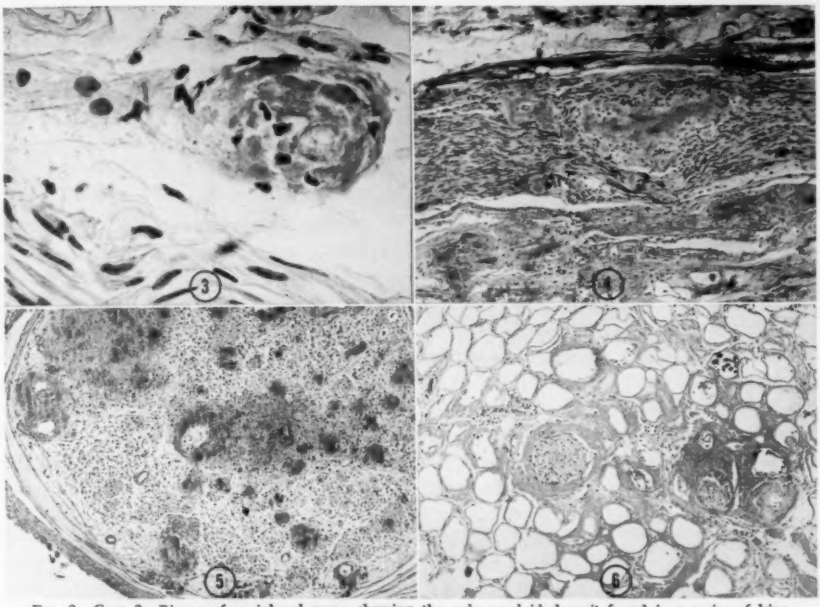


FIG. 3. *Case 2.* Biopsy of peripheral nerve showing the only amyloid deposit found in a series of biopsies. It is located in the perineurium. Congo red stain.
FIG. 4. Autopsy. Longitudinal section of nerve with abundant amyloid deposition within nerve and in surrounding supporting tissues. Congo red stain.
FIG. 5. Autopsy. Cross section of large nerve clearly demonstrating the intramural vascular deposition and extension to surrounding stroma effacing nerve fibers. Congo red stain.
FIG. 6. Autopsy. Section of pericardium showing encasement of small nerve bundles and vessels. Hematoxylin and eosin stain.

weakness of all extremities, much more marked at the periphery and all tendon reflexes were absent. Abdominal reflexes were present. Light touch and pain sensations were diminished below the mid-shin and on the fingers. Vibratory and position sensibilities were impaired in the feet.

He was readmitted to the hospital on November 15, 1954 and again on December 30, 1954. Weakness had greatly increased so that he was virtually bedridden, and sensation was diminished to groins and upper arms. His hands were useless because of weakness and sensory impairment.

During his hospital stay extensive laboratory studies were carried out in an effort to determine the etiology of his disease. Urine and blood studies were normal. Blood chemistries were performed repeatedly and all were within normal limits. Blood sedimentation rate was 4 mm./hour. Serologies were negative. Spinal fluid protein was 140 mg. per cent. Liver function tests showed a 4 plus cephalin flocculation and thymol turbidity 3.8 units. On congo red test 85 per cent of the dye was retained in the serum at the end of 60 minutes. Twenty-four hour urine examinations were negative for coproporphyrin, porphobilinogen, lead, and Bence-Jones protein. Examination of the hair and nails was negative for arsenic. Electrocardiogram was abnormal due to left bundle branch block with associated T-wave changes.

Repeated biopsies of peripheral nerves, muscle, skin, liver, and gums showed no evidence of amyloid deposition. The patient had had laryngeal polyps removed at another hospital. A review of the pathologic specimen showed fragments of larynx with focal ill-defined swelling characterized by a stromal homogenization of collagen with small, irregu-

lar, homogeneous, eosinophilic stromal deposits (figure 7). This material was also found within the walls of small vessels, thickening them in eccentric fashion. A congo red stain performed on a single available section after decolorization disclosed a variable metachromasia of the lumpy material and of the intramural vascular deposits. These changes were entirely in keeping with a so-called amyloid tumor of the larynx.

DISCUSSION

In view of the more widespread interest in primary amyloid disease in recent years and increasing reference to it in the literature, it seems unnecessary here to dwell on the basic pathologic features of amyloidosis, the theories and experimental work concerning its fundamental nature, and its relationship to secondary amyloidosis which have been discussed adequately elsewhere.[1–3] Primary amyloidosis is essentially a disease of mesenchymal tissue, whereas secondary amyloidosis chiefly affects parenchymatous organs.[1] It is this predilection for involvement of mesenchymal tissue which enables one to establish a diagnosis of amyloid polyneuropathy clinically, and it appears from a review of the literature that the heart and larynx are most frequently involved in primary amyloidosis.

Primary amyloidosis is a disease occurring most frequently in later life, having its onset around the fifth decade or later. A familial type beginning earlier in life has also been reported. Males appear to be afflicted three times as frequently as females.[4]

We have reported three cases of poly-

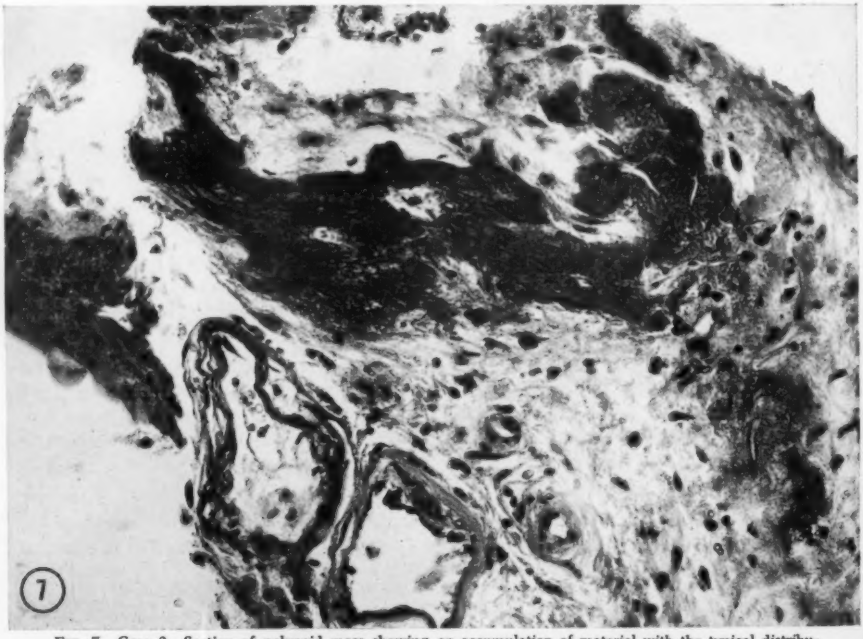


FIG. 7. *Case 3.* Section of polypoid mass showing an accumulation of material with the typical distribution of amyloid but staining weakly with congo red after decolorization. Hematoxylin and eosin stain.

neuropathy due to primary amyloidosis. There were two males and one female. The ages of these patients at the time of first examination were 50, 54, and 59. In each patient, however, a change in the voice or a clinical suggestion of heart disease preceded the onset of the neuropathy. Case 1 had had clinical evidence of cardiac disease some three to five years before the onset of a neuropathy. Cases 2 and 3 had had a change in voice consisting of hoarseness and narrowing of range for some years before any symptoms of nervous system involvement appeared. By the time of initial examination, however, all manifested evidence of involvement both of the larynx and heart in addition to a neuropathy.

The neuropathy itself always began with involvement of the lower extremities. Pain in the soles of the feet or in the calves was prominent as an early symptom in all; burning pain was reported in two of the three cases. Early in its onset the neuropathy was asymmetrical, the pain and numbness or weakness beginning first in one extremity, followed in a few months by similar involvement of the other limb. In like manner involvement of the upper limbs might begin in an asymmetrical fashion, but within a short time there was a symmetrical involvement of both upper and lower extremities with little difference in motor or sensory defect.

There was no particular feature of the neuropathy itself in amyloid disease to differentiate it from a polyneuropathy of other cause. Weakness was most profound distally and eventually atrophy, again more marked distally, appeared. There was a marked disturbance of all modalities of sensation more prominent in distal parts and shading off in the proximal segments. This sensorimotor defect became a grave disturbance, progressing relentlessly week after week.

Death of two of the patients resulted from congestive heart failure. The third patient is still living but bedridden because of profound weakness.

The nature of the hoarseness and narrowing of the vocal range in these patients was not determined clinically in examinations by competent otolaryngologists. In one patient the change in voice was thought to be functional. In another laryngeal polyps were discovered, but initial histologic examination did not reveal evidence of amyloidosis. Only after thorough reexamination of this specimen some ten months later was the diagnosis of amyloidosis established, an experience recalling that of DeWolf and Clarke.[5] In the third patient the otolaryngologist reported an amber color of the vocal cords attributed to early icterus, although there was no such evidence of icterus either on clinical or laboratory evidence. It is of interest, however, that both McCall and Fisher[6] and Stark and New[7] report that the larynx in primary amyloidosis may have a "definite yellowish color."

Involvement of the larynx in primary amyloidosis is well known and has been discussed recently by McCall and Fisher[6] and Stark and New.[4,7] The larynx may be involved in one of two ways, either by deposition of amyloid as a local tumor, or by deposition more diffusely through the larynx without tumor-like swelling. They state that the symptoms may be either hoarseness or dyspnea.

Frequent reference to primary amyloidosis of the heart has been made in the literature. Of special interest to us have been the reports of electrocardiographic changes in primary amyloid dis-

ease. Parker and co-workers,[8] Pruitt, Daugherty, and Edwards,[9] Ohliger and Harmos,[10] Thomashow, Angle, and Morrione[11] and others discuss the electrocardiographic abnormalities. They indicate that these are not characteristic findings but rather minor and nonspecific abnormalities such as low QRS complexes, T-wave changes, auricular fibrillation, conduction defects, right or left axis deviation, and various bizarre changes. These are entirely in agreement with our findings.

It is interesting to note the frequency of involvement of heart and/or larynx in other cases of amyloid polyneuropathy reported in the literature. Thus, Strich and Wade[12] reported a patient with congestive heart failure and a peripheral neuropathy. Earlier in his illness he had complained of dyspnea prior to the appearance of frank heart failure, but it is not clear from the report if this was due to cardiac involvement. Findley and Adams[13] report a case of primary amyloidosis with clinical involvement of heart and peripheral nerves. The patient of Fisher and Preuss[14] first presented with dyspnea and weakness of his legs. At the time of his first admission an abnormal electrocardiogram was recorded.

Kernohan and Woltman[15] attribute the neurologic symptoms in amyloid polyneuropathy to ischemic degeneration of the nerve, caused by involvement of blood vessels with amyloid. Ritama and Bjorkesten[16] felt that the part played by the amyloid deposits in producing the symptoms and signs, however, was insufficiently elucidated and inclined toward an inflammatory pathogenesis. We believe that the course of amyloid polyneuropathy, a symmetrical neuropathy beginning in the lower limbs and ascending, is difficult to explain wholly on a compressive or ischemic basis and would suggest some additional toxic or metabolic factor in operation.

Recently, Andrade[17] and Kantarjian and DeJong[18] have reported a familial form of primary amyloidosis with involvement of the peripheral nerves. These cases have occurred in young people in the second or third decade with an insidious onset of a sensorimotor neuropathy associated with gastrointestinal disturbances, ocular changes, sexual and sphincter changes, and other evidence of autonomic and endocrine disorders. We believe these represent a distinctly different clinical entity from the group we have presented in that there is a familial tendency, earlier age of onset, and associated involvement of a different type. It is probable that the case of DeNavasquez and Treble[19] is an example of this familial type of amyloid polyneuropathy.

The difficulty of establishing a diagnosis of primary amyloidosis has been noted by many. Repeated biopsies may be negative. The congo red test is often negative, especially in primary amyloidosis where the pigment does not have the marked affinity for the dye as in secondary amyloidosis. It is believed that in amyloid neuropathy the involvement of other organs, particularly the larynx and heart, will justify the diagnosis despite lack of corroborative evidence early in the course of the disease.

CONCLUSION

Observations on three cases of amyloid polyneuropathy lead us to conclude that a clinical diagnosis of this disease may be made. Verification by biopsy may be difficult. In our cases the clinical diagnosis led to repeated biopsies and reexamination of the pathologic material and thus to the verified diagnosis.

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■ If we compare this conclusion with this well-known fact, that there are several, I may even say many, pathological cases, showing that in man an alteration of the posterior columns has caused nothing but a loss or a diminution of voluntary and reflex movements, we find an appearance of contradiction which in reality, however, does not exist, as I will show in another lecture.

After having divided transversely the two posterior columns and the posterior gray horns, we find that there is an evident, although very slight diminution of voluntary movements. But now, if instead of dividing this part of the spinal cord, we divide the whole of this organ, except this part, we find that voluntary movements are completely lost. It seems, therefore, that there are some conductors for voluntary movements in either the posterior horns or the posterior part of the lateral columns or in both; but it appears also that there is but a small number of such conductors in either of these parts.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Chlorpromazine and Human Spasticity

An Electromyographic Study

J. V. Basmajian, M.D. and A. Szatmari, M.D.

A PRELIMINARY REPORT has been published of electromyographic findings in 13 spastic patients who were given 50 mg. of chlorpromazine (Largactil) intravenously under experimental conditions.[1] As stated then, there was a dramatic abolition of spasticity for about two hours in 11 of the 13 subjects and appreciable improvement in the other two. There was, however, no impairment of whatever voluntary motor power the patients retained.

Since then we have broadened our experience, having added to our series four adult paraplegics and a 15 year old boy with cerebral palsy. Five cases of choreoathetosis and one case of parkinsonism have also been studied because of an earlier observation that parkinsonian tremor was temporarily abolished in a spastic patient. In all the newer cases the dosage has been reduced to 0.5 mg. per kg. of body weight. The electromyographic technic and experimental procedure have remained essentially the same as before. Recordings of resting muscles, tendon reflexes, voluntary contractions, irradiation phenomena, and clonus were made before the injection of chlorpromazine and at measured intervals afterwards. Concurrent observations were made on the state of consciousness and affective state, and on any associated phenomena. All the patients were kept recumbent for at least an hour.

RESULTS

Spasticity. Among 18 patients with spasticity due to an upper motor neuron lesion, complete abolition of spasticity occurred in 15 cases and a marked (though incomplete) effect was seen in the remaining three (figures 1 and 2). The boy with cerebral palsy was especially interesting because the full effect persisted in him far beyond the usual two hours and was still marked after 20 hours. During this time his voluntary power was unimpaired (figure 3). This last observation has been true in all cases, with the possible exception of one quadriplegic who reported inability to move his partially involved upper limbs

From the department of anatomy, University of Toronto, and the Ontario Hospital, Toronto.
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for 15 minutes after the injection. This phenomenon disappeared rapidly and spontaneously, and the patient was able to perform purposeful movements without spasticity for more than a hour afterwards.

In contrast with the influence of chlorpromazine on the hypertonic reflexes of spastic patients, the knee jerk of a normal person remains unchanged or may even be increased (figure 4).

Parkinsonism. Parkinsonian tremor and rigidity were completely abolished within three minutes of the injection in two patients. In one patient they returned gradually and spontaneously at about two hours. In the other they returned promptly upon the intravenous injection of Lobeline (0.01 gm.) 25 minutes after the injection of chlorpromazine.

Choreoathetosis. There was absolutely no effect, good or bad, on involuntary movements, power, or reflexes in the five

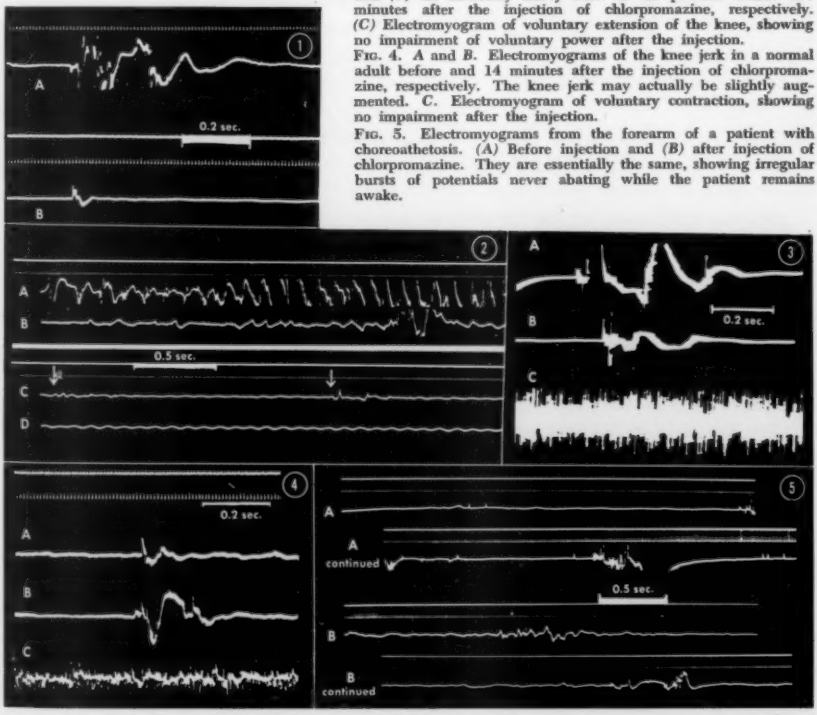
FIG. 1. Electromyogram of the knee jerk of a paraplegic patient *(A)* before and *(B)* 12 minutes after the intravenous injection of chlorpromazine. The knee jerk has become normal.

FIG. 2. Electromyogram to demonstrate knee clonus in another (quadriplegic) patient. Concurrent tracings *A* and *B* are from the right quadriceps and right triceps brachii respectively, before the injection. Note the spread of excitation to involve the upper limb. *C* and *D* are from these muscles 10 minutes after the injection of chlorpromazine. Arrows mark two vigorous attempts to start knee clonus with little success and no spread to the upper limb.

FIG. 3. *A* and *B*. Electromyograms of the knee jerk in a boy with cerebral palsy. *(A)* A very light tap before and *(B)* an extremely heavy blow to the patellar tendon five minutes after the injection of chlorpromazine, respectively. *(C)* Electromyogram of voluntary extension of the knee, showing no impairment of voluntary power after the injection.

FIG. 4. *A* and *B*. Electromyograms of the knee jerk in a normal adult before and 14 minutes after the injection of chlorpromazine, respectively. The knee jerk may actually be slightly augmented. *C*. Electromyogram of voluntary contraction, showing no impairment after the injection.

FIG. 5. Electromyograms from the forearm of a patient with choreoathetosis. *(A)* Before injection and *(B)* after injection of chlorpromazine. They are essentially the same, showing irregular bursts of potentials never abating while the patient remains awake.



patients with choreoathetosis as long as they remained awake (figure 5).

Levels of consciousness. Most of the 24 patients at least felt drowsy after the intravenous injection. Although six became quite somnolent, they could be aroused easily. There was no relationship between levels of consciousness and the effect of the drug on spasticity and on parkinsonian tremor.

DISCUSSION

There is no doubt that chlorpromazine given intravenously abolishes spasticity in almost all cases, and apparently it has a similar action in parkinsonism. However, two very real problems emerge: 1) How can the clinician adapt this knowledge to therapy? 2) What is the mode of action of the drug, which heretofore has not been suspected of affecting the motor pathways to voluntary muscle?

Therapy

We have had neither the opportunity, the facilities, nor the inclination, in a department of anatomy, to develop a treatment schedule for patients with spasticity. This would be better left to others. From our limited experience, we would suggest that ordinary oral doses alone may prove disappointing. On the other hand, since this is the first drug ever to show such marked action on this severe disability, a full trial seems to be warranted. At least there is reason to alter the generally pessimistic view taken of spasticity. There are many compounds related to chlorpromazine, one of which may prove to be the final answer.

Insofar as parkinsonism is concerned, our very limited experience again suggests caution. Therapeutic use of the drug may not prove feasible. Indeed, there have been cases of parkinsonism which actually developed during chlorpromazine treatment of mental illness. We have examined one such patient electromyographically, and found the typical picture. Recently Richman and Tyhurst[2] reported 12 cases of parkinsonism following administration of reserpine. In such cases, the tremor disappears upon discontinuing therapy with either drug.

Mode of Action

Here, perhaps, we have the real interest and significance of our findings. Chlorpromazine has been suspected and generally accredited with acting on synaptic nuclei of the involuntary or vegetative nervous system. Recently it has been incriminated as a direct poison of muscle fibers when given in large, direct, intra-arterial doses to sciatic-gastrocnemius preparations in the cat,[3] and when tested with isolated nerve-muscle preparations.[4] Yet, except for a bizarre transient paralysis of partially involved muscles in a quadriplegic, all our evidence suggests that therapeutic doses do not have a peripheral effect. The paradox of parkinsonism being relieved by chlorpromazine in some cases and being brought on when the drug is given to some mentally ill patients adds further problems.

At present we can only speculate. Spasticity is now considered as an imbalance of the facilitatory and inhibitory centers located in the lower pontobulbar segments of the brainstem. These in turn are influenced by the central activating system described by Magoun and his colleagues. We accept the concept that spasticity is due directly to an enhancement of the bulbar facilitatory systems following the loss of the inhibitory or suppressor systems. This

leads to a facilitatory influx to the spinal cord conducted by reticulospinal and vestibulospinal tracts. The effect of chlorpromazine on the motor system seems to be a depression of this facilitation. Although more conclusive evidence is needed, this effect is likely to be at the level of the brainstem rather than in the spinal cord, because the stretch reflex of normal or nonspastic subjects is not depressed by chlorpromazine. Since actually there may have been an increase in the normal stretch reflex, further work must be done with normal subjects. If chlorpromazine does enhance the stretch reflex of normal persons, we would be forced to conclude that it does so by depressing the inhibitory downward influence of the reticular formation more than the facilitatory influence. This would fit in with a current concept that the inhibitory influences are a more "recent" acquisition and are more easily destroyed, for example, by an injury to the spinal cord.

Unlike spasticity, where the spinal cord is released from the coordinative centers in the brainstem, extrapyramidal conditions are caused by release of the motor cortex proper (Brodmann 4) from the premotor cortex (Brodmann 6 and 4s) via striopallidonigrothalamic pathways (Fulton and Bucy). In other words, extrapyramidal conditions exhibit selective dissociation of various cortical areas of motor function. Therefore, chlorpromazine will affect extrapyramidal disorders only when cortical functions are depressed. In view of this, it is not surprising that our cases of choreoathetosis are unaffected by the drug except when actual sleep is allowed to occur.

Clinically, chlorpromazine decreases anxiety and tension without necessarily affecting awareness, and in the electroencephalogram it causes mild progressive synchronization of the electrical pattern. Cerebral vigilance is a condition of critical reactivity, of spontaneity of behavior, and of complete adaptive and conscious integration. In order that wakefulness may be maintained, there is a need for a continuous facilitation of cortical and diencephalic neuronal networks.[5] The ascending reticular system of Magoun seems to activate the cerebral cortex as a whole, with particular reference to the state of alertness. This effect is mediated by nonspecific thalamocortical projections which are as yet poorly understood. Chlorpromazine appears to depress this system selectively, thus decreasing "tension" of the cortex, just as it decreases the "tension" in the spinal cord.

The paradox of parkinsonism—where the drug can both abolish and cause the tremor—remains to be explained. In 1948 Ward, McCulloch, and Magoun[6] reported the experimental production of a rhythmic tremor at rest in monkeys by placing lesions entirely below the basal ganglia and destroying part of the mesencephalic and pontile tegmentum. They suggested that the source of tremor at rest was the unrestrained rhythmic activity of the reticular formation acting downwards. If this thesis is applicable to human parkinsonism, then the explanation for the abolition of tremor by chlorpromazine is not unlike that for the abolition of spasticity; that is, the drug depresses the downward influence of the unrestrained reticular formation.

Finally, we may postulate the hypothesis that, in certain sensitive persons, continued doses of chlorpromazine may interrupt or depress the same pathways from basal ganglia to reticular formation as were interrupted by experimental le-

sions in monkeys. Obviously, combined experiments with chlorpromazine and stereotactic apparatus are needed. Perhaps it would be naive to hope that the problems solved will outnumber those that are created anew.

SUMMARY AND CONCLUSIONS

Our original electromyographic observations on the effect of chlorpromazine on human spasticity have been expanded. In 15 of 18 patients dramatic abolition of spasticity for about two hours was obtained by the rapid intravenous injection of not more than 50 mg., with lesser effects in the other three. In a boy with cerebral palsy the effect lasted more than 20 hours.

Voluntary muscular activity was unaffected except in one quadriplegic who reported a brief transient paralysis of a partially-affected limb.

The effects are not related to the state of consciousness. Most patients remained highly cooperative, though some became quite sleepy.

No effect on the involuntary movements or the reflexes was recorded in five cases of choreoathetosis and no depression was seen in a normal subject's neuromuscular responses.

Two cases of parkinsonian tremor were relieved temporarily, in contrast to the occasional appearance of such a tremor in long term therapy for psychosis with chlorpromazine and reserpine.

The possible modes of action are discussed. The effect is apparently a depression of overbalanced facilitatory influences of the brainstem reticular nuclei.

The authors wish to thank those physicians who referred patients, especially Drs. A. T. Jousse and W. A. Hawke.

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■ Now, as regards the question, which of these parts of the spinal cord is the principal channel for the orders of the will? We cannot give a very positive opinion. We can, however, state that of these three parts – the lateral columns, the anterior columns, and the gray matter – each of the last two seems to have a greater share in this function than the first. Besides, the gray matter appears to have as great a share as the anterior columns, and in the gray matter the most important parts seem to be those in the anterior half of the cord.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Cervical Myelopathy

A Contribution to Its Pathogenesis

Edwin Clarke, M.D., M.R.C.P. and J. H. Little, M.B., B.S., D.C.P.

ALTHOUGH KNOWLEDGE of the clinical picture presented by cervical myelopathy is increasing,[1–5] ignorance concerning the details of its pathogenesis and pathology is still considerable. One of the most perplexing problems is that, despite the almost universal occurrence of cervical spondylosis in elderly persons,[6] only a small proportion develop spinal cord compression.

Any case, therefore, that increases our knowledge of these aspects of the condition is of importance and worthy of record. The following is such a case:

CASE REPORT

An 81 year old housewife was admitted to the hospital on November 29, 1954, and died there nine weeks later.

She was first seen in September 1949, five years before death, when she complained of pain in the shoulders of a few weeks' duration. Apart from slightly limited active movements and crepitus in the shoulder joints, there were no other abnormal findings. Roentgenograms confirmed the presence of degenerative disease in these joints. Physiotherapy produced temporary improvement, but two years later when admitted to the hospital, pain in the shoulders was more severe and she had tingling in the hands. She was becoming increasingly disabled by generalized joint disease. On examination neck extension and rotation were painful and limited. There were more advanced degenerative changes in the shoulder joints, with moderate wasting of the muscles around them. The small muscles of the hand were slightly wasted but there was no corresponding weakness. Power in the arms could not be evaluated because of pain-guarding but in the legs it was normal. Reflexes were normal and the only sensory modality definitely affected was vibration sense which was absent in all limbs; she was, however, a very poor sensory witness. The blood pressure was 210/100. Roentgenograms of the cervical spine showed severe spondylotic changes.

She again improved for a time with physiotherapy and encouragement, but then gradually became less and less active. In January 1953, two years before death, she was found to have increased tone and reflexes in all limbs and a right extensor plantar response.

On her final admission she was completely bedridden. Considerable mental deterioration had taken place and she was occasionally incontinent of urine and feces. Neck movements were limited in all directions. There was generalized wasting of the limbs, with increased tone in the arms and decreased in the legs. Some forearm, wrist, and finger movements were possible, but in the lower limbs only slight dorsiflexion of the feet was present. Finger flexion accompanied the biceps and supinator jerks which were sluggish; the leg reflexes were diminished or absent and both plantar responses were extensor. All sensory modalities were affected below a level at C3. There was a large sacral bed sore. The blood pressure was now

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FIG. 1. Roentgenogram of cervical spine, lateral view. Gross spondylotic changes at all levels. Anomaly and displacement of C2.

120/80. Cervical spine roentgenograms (figure 1) showed gross degenerative changes at all levels, especially at C5-6. The body of C2 had moved forward on that of C3 and its spinous process and lamina appeared to be abnormally small. It was only in retrospect, however, that this impression was confirmed.

The patient remained in this state until her death on February 6, 1955, due to congestive cardiac failure and complications of the quadriplegia.

AUTOPSY

There was widespread evidence of benign hypertensive degenerative cardiovascular disease. Many joints showed severe degenerative changes.

The cervical spinal column and contents were removed in one piece. As soon as the laminae were cut away, a sharply delineated compression of the posterior surface of the dural tube was visible (figures 2 and 3) at the level of C2-3. This was caused by the laminae of C2 together with the ligamentum flavum between it and the laminae of C3, which were protruding into the spinal canal. The dura mater at this level was thickened (figure 4) but not adherent to the compressing structures.

The dural tube was next removed to reveal the anterior wall of the spinal canal. At the disk space between the bodies of C2 and C3 there was a prominence due to a slipping forward of C2 upon C3 (figure 4) and the formation of a "step" between the posterior surfaces of these vertebrae. It projected posteriorly into the spinal canal to indent the anterior surface of the cord (figure 5), the dura mater being slightly adherent at this point. The spinal cord and its meninges had thus been severely compressed between anterior and posterior lesions situated at the same level (figure 4). They combined to nip the cord and produce a remarkable degree of thinning (figure 6), which was so severe that on holding the cord to the light a translucent area could be seen at C3 (figure 7). Despite advanced intervertebral disk degeneration at all levels (figures 1 and 4), encroachment upon the spinal canal elsewhere had not taken place.

By inspection of the bones and the roentgenograms of the specimen (figure 8) and patient (figure 1), the following conclusions concerning the cervical vertebrae were possible:

1. Whereas it is generally accepted that the laminae and spinous process of C2 are bigger than those of all other cervical vertebrae,[7,8] they were smaller in this case (figure 8). It was difficult to appreciate this adequately from the roentgenograms of the patient (figure 1) because of some rotation of the neck and the presence of soft-tissue calcification around the spines of C2 and C3 and also opposite the process of C5; the latter changes are not uncommon in elderly persons and were first noted by Bársony.[9] The under surface of the lamina of C2 was in close apposition with the superior surface of that of C3 and a false articulation had developed between them. Figure 8 reproduces a roentgenogram of the removed laminae showing the relative smallness of C2.

2. The apophyseal articulations between the axis and C3, although somewhat asymmetrical, were not otherwise abnormal. An anomaly such as Kremser[10] described was not present.

3. The body of C2 was of normal size and the displacement anteriorly, seen on roentgenograms of the patient, was confirmed (figure 4).

FIG. 2. Cervical spine from behind, with laminae removed. Indentation of dural tube and posterior compressing lesion shown. FIG. 3. Cervical dural tube, lateral view, showing posterior indentation at C2-3. FIG. 4. Cervical spine and cord reconstructed after sagittal section. Anterior and posterior compressing lesions can be seen. Dura thickened posteriorly. FIG. 5. Cervical dural tube, anterior view, showing indentation at C2-3. FIG. 6. Sagittal section of spinal cord with dura mater folded back. Severe compression shown. FIG. 7. Spinal cord silhouette showing area of extreme thinning. Dura removed from right half only.

Histologic examination of the spinal cord (Weigert-Pal) showed complete demyelinization of fibers at the level of the compression. Similar preparations above and below this point revealed almost complete fiber loss in the region of the pyramidal tracts and a less severe involvement of the posterior columns.

DISCUSSION

The pathologic features of cervical myelopathy have been described by a number of investigators.[3,11–13] Although these authors differ in their conception of the spinal cord changes and the exact

role of compression and arachnoiditis, there seems no doubt that the common factor is cord compression, and adequate evidence for its production by intervertebral "bars" (made up of degenerating disk, osteophytes, and ligament) damaging the anterior surface of the cord has been produced. Anterior compression was present in this case also and was due to the "step" between C2 and C3 (figure 4). However, there was an additional factor present, for, as well as the anterior cord lesion, the posterior surface was also deformed due to pressure on it from behind.

When the neck of a normal person is fully extended, corrugation of the posterior wall of the spinal canal is produced by the ligamentum flavum bulging forward; at the same time, protrusion of the intervertebral bars is increased, as also happens in the lumbar region.[14] At autopsy in these persons minor degrees of compression of the posterior surface of the spinal cord due to permanent irregularities in the ligamentum flavum can be seen, but, like the anterior indentations, they are mild and symptomless. Taylor[15] has shown by roentgenographic studies of cadavers that corrugation of the ligamentum flavum occurs in the normal, and Walker[16] has depicted the same process, although less convincingly. In addition, Schneider and co-workers[17] have recently discussed the same happenings in acute hyperextension injuries of the neck, where the cord is damaged from in front and from behind without bony injury occurring. These authors all suggest that pressure on the cord from behind as well as from in front, if acting at or near the same level, will produce severe cord damage.

This mechanism is admirably illustrated by the case presented here and was made possible by the slipping forward of the second upon the third cervical vertebra. Thus the "step" between the posterior surfaces of the bodies formed the anterior lesion, and the laminae of C2 which had been dragged forward with the body, together with corrugation of the ligamentum flavum (figure 8), produced the posterior component. The cord imprisoned between these two unyielding structures suffered intermittent compression, presumably maximal, when the neck was in a position of extension. Eventually severe thinning and almost complete severance of the cord took place (figures 4, 6, and 7) and the dura mater became thickened posteriorly and adherent anteriorly. This sequence of events presumably proceeded at a slow pace because there were no acute episodes recorded in the patient's history. In view of the severe cord lesion (figure 7) it is remarkable that she had any function at all below her neck. And yet some distal limb movements were possible, sensory changes were by no means complete, and sphincter control was not entirely lost.

Despite roentgenographic evidence of severe generalized cervical spondylosis (figure 1), the gross specimen (figure 4) showed that cord compression was occurring at only one level (C2 to C3). This finding is in keeping with the well-known fact that the radiologic appearance of the cervical spine cannot be correlated directly with the clinical picture of cervical myelopathy and that the majority of elderly subjects have cervical spondylosis but no evidence of myelopathy.

To find so localized a cord lesion as in our case is relatively unusual in this disease and, in addition, involvement at the C2 to C3 level is very rare. An

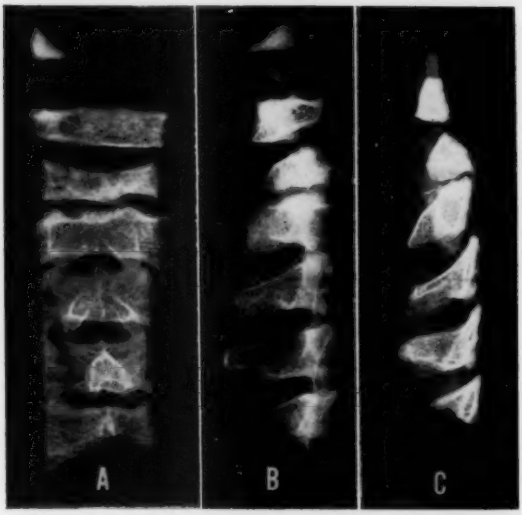

FIG. 8. Roentgenograms of laminae. *A* and *B*. Axial and lateral views showing small C2 lamina and spine (piece of occipital bone and C6 laminae included). *C*. Lateral view of half specimen to show protruding ligamentum flavum.

explanation for these unusual findings was therefore sought. In a large series of cases,[18] one of the conditions producing this type of lesion was a congenital lesion of the cervical vertebrae, and Brain and co-workers[3] also refer to such a possibility.

The laminae and spinous process of the axis in the present case were found to be smaller than normal (figures 1 and 8), but there was no evidence of trauma or other exogenous factors. Although MacAlister[19] in a detailed account of the axis did not mention this anomaly, he examined only a small number of specimens, and Crouzon and Liège[20] were dealing mainly with the relatively common Klippel-Feil syndrome and its modifications. Congenital anomalies of the arches of the vertebrae are not infrequent, especially in the lumbar region,[21] but similar lesions occur in the cervical spine.[22,23] Roentgenograms of the rest of our patient's spine, unlike the case of Rathke,[24] revealed no other abnormalities. Two examples of congenitally small laminae of C3 have been encountered,[18] and it is suggested that a similar malformation involved the axis in the present case.

The sequence of events in the patient can therefore be reconstructed. She had a congenital anomaly of the arch of C2 which produced no symptoms or signs during most of her life. As she aged, however, cervical spondylosis due to degenerative changes in the intervertebral disks developed and a potential instability that was previously well compensated now became apparent. The deformity between C2 and C3 gradually appeared and the cord damage ensued.

Our knowledge of major congenital malformations of the cervical vertebrae is extensive, but little has been done to investigate the less obvious ones. Although they may be rare it is important to be on the lookout for such bony anomalies, which are known to be more common in the upper portion of the cer-

vical spine. They are presumably symptomless in many instances, but the addition of spondylosis may induce instability and the progression of events as postulated in the present case. It is possible that this is one of the factors that determines why only a small proportion of those developing cervical spondylosis show features of cord disease. On the other hand, the presence of a congenital anomaly may produce instability of the spine and therefore may be responsible itself for the appearance of spondylosis, which in some cases leads to cord or root involvement.[3,18] Unlike our patient, however, this usually begins earlier in life.

Overton and Grossman[25] have investigated the anatomic variations of the articulations between C2 and C3 and, together with Kovács,[26] claim that headaches may be produced by C3 root or vertebral artery compression. It is of interest to note that Portal[27] suggested that the latter factor might be responsible for disturbances of cerebral circulation. However, despite the localization of the lesion in our patient, she had not experienced headaches and the mental aberrations were due to senile arteriosclerotic degeneration. Furthermore, the asymmetry of degenerative changes in the apophyseal joints stressed by these authors may be seen in persons without any symptoms and each lesion described by them, either developmental or acquired, may be clinically silent.[28]

The obvious clinical consideration in the type of case under discussion is the role of surgery. If the lesion could be detected early enough, removal of the compressing laminae and ligamentum flavum would decompress the cord and prevent its being pinched. Some improvement might be expected, or at least the progression of the disease might be stayed. Further instability of the spine may, of course, result. In any case, full extension of the neck would have to be forbidden, if necessary by the application of a collar. The responsibility for achieving success, however, rests with the clinician, who must be aware of this type of lesion so that the diagnosis may be made at an early stage. Tomography of the cervical spine may help and more adequate myelography is necessary. Views of the opaque material in the cervical canal with the patient in the lateral position, as well as "full-column" myelography,[29] will give more information concerning the posterior compressing lesion.

SUMMARY

A case of cervical myelopathy is described in which the spinal cord was severely damaged by anterior compression due to an intervertebral ridge and posterior compression due to protruding laminae and ligamentum flavum, both acting at the same level (C2-3). It is suggested that this lesion was the result of cervical spondylosis appearing in the presence of symptomless congenital smallness of the laminae and spinous process of the axis. Although this may be one of the less common factors in the production of spondylitic myelopathy, closer radiologic and pathologic examination of the cervical spine in health and in disease is necessary to evaluate its relative importance.

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■ What is the place of decussation of the various posterior roots of a pair of nerves? I have said, in the preceding lecture, that the fibres which enter the spinal cord, from the posterior roots, are distributed, in the nervous centre, in such a way that some are going upwards, some downwards, and some transversely. There are, therefore, ascending, descending, and transversal fibres. Now, all these fibres reach the central gray matter, after a short way, above or below their place of entrance, and almost at once they decussate. A great many experiments show that this must be the arrangement of the conductors of sensitive impressions.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System,* published in 1860.

Neurologic Manifestations of Nasopharyngeal Tumors

Herbert E. Rosenbaum, M.D. and William B. Seaman, M.D.

SOME YEARS AGO Woltman drew attention to a general lack of appreciation of the neurologic symptomatology associated with the growth of nasopharyngeal tumors.[1] Since his interesting and detailed paper, few other reports have appeared in the neurologic literature. Meanwhile these tumors have increased in incidence and now account for about two per cent of all cancers.[2] As with cancer in general, the hope for a good prognosis is dependent on early recognition. Because the earliest presenting signs of a nasopharyngeal malignancy are frequently those attributable to its intracranial extension, it behooves the neurologist in particular to be familiar with the marked variability which may characterize this condition.

For these reasons a review of diagnostic considerations emphasizing the anatomic relationships of the structures involved and the roentgenographic findings may prove helpful in preventing delay in making a correct diagnosis. The material presented is based on the findings in 24 patients with nasopharyngeal tumors who presented initially with neurologic signs (table 1). These were seen at Barnes Hospital for diagnosis and/or therapy during the past five years, with the exception of three examined prior to that time. A total of 39 cases with no neurologic complaints have been seen since 1950.

ANATOMIC CONSIDERATIONS

A thorough knowledge of the anatomy and gross pathology of these tumors is of more than academic interest to the neurologist when one considers that neurologic symptoms are the initial ones in at least 25 per cent of these tumors, and that the nervous system is involved at one time or another in over one-half of them.[3–5] The reason for frequent intracranial extension of these tumors is that the usual site of origin is in close proximity to the base of the skull, and particularly to the foraminae lacerum and ovale.[3] This is of even greater importance when one realizes that the sixth cranial nerve lies only two centimeters from the fossa of Rosenmüller, which is the site of origin of the majority of these neoplasms. Figure 1 illustrates the re-

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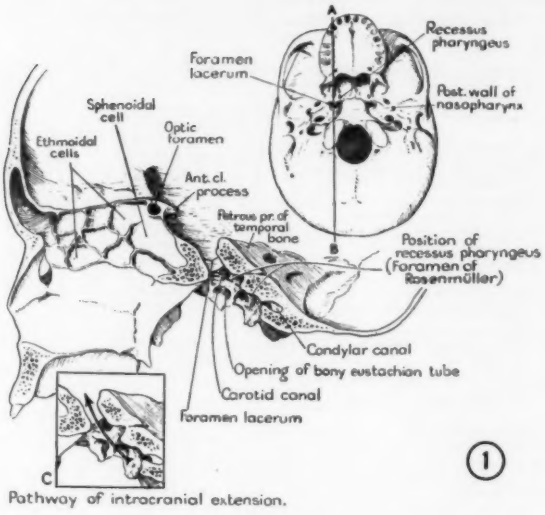
Read at the seventh annual meeting of the American Academy of Neurology, Houston, Texas, April 28, 1955.



Pathway of intracranial extension.

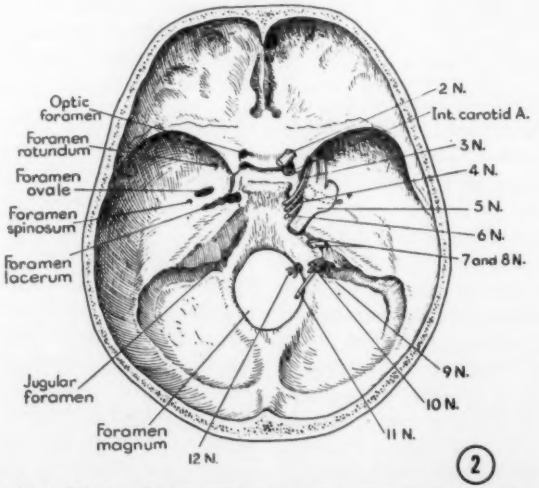


FIG. 1. The fossa of Rosenmüller lies immediately beneath the foramen lacerum, thus allowing direct access for intracranial extension of nasopharyngeal cancer. The large diagram is a sagittal section along the line *A-B* through the foramen lacerum, illustrating the juxtaposition of the lateral wall of the nasopharynx, the foramen lacerum, and the cranial cavity. Insert *C* demonstrates the direct pathway of the extension.

FIG. 2. Diagrammatic representation of the internal view of base of the skull, showing the juxtaposition of the foramen lacerum and the third, fourth, fifth, and sixth cranial nerves. Nasopharyngeal cancer extending intracranially through the foramen lacerum comes in contact first with the sixth cranial nerve. The growth may then spread forward through the superior orbital fissure into the orbit or backward into the posterior fossa to involve all the cranial nerves.

TABLE 1
FINDINGS IN 24 CASES OF NASOPHARYNGEAL TUMORS

Case No.	Age	Sex	Initial Symptom	Neurologic Involvement	Positive Roentgenogram	Tumor Type
1	61	M	Bitemporal pain	Left XII	yes	Epidermoid ca.
2	36	M	Left facial pain	Left II, V, VI, VII, IX, X, XII, Horner's	no	Epidermoid ca.
3	57	F	Right facial pain	Right II, III, IV, V, VI, VII	yes	Epidermoid ca.
4	64	M	Hoarseness	Right IX, X, XI		Transitional cell ca.
5	55	M	Pain in left ear	Left V, VI, VII, IX	yes	Epidermoid ca.
6	61	M	Hoarseness	Right IX, X, XII, Horner's		Epidermoid ca.
7	43	M	Pain in right ear, diplopia	Right VI	yes	Epidermoid ca.
8	58	M	Pain in right eye, right facial epistaxis and numbness	Right V, VI, IX, X, XI, XII, Left VI, Right hemiparesis	no	Lymphoepithelioma
9	58	M	Left-sided weakness and nasal stuffiness	Right Horner's, left hemiplegia		Transitional cell ca.
10	47	M	Headache, hoarseness	Right V, VI, IX, X, XII	yes	Epidermoid ca.
11	55	M	Right ear pain	Left VI		
12	18	M	Headache, nasal stuffiness	Left III	yes	Lymphoepithelioma
13	61	M	Severe headache and right facial pain	Papilledema, right Horner's, left hemiparesis		Undiff. ca.
14	75	M	Numbness of left lower face	Left V		Epidermoid ca.
15	47	M	Complete nasal obstruction with nose bleeds	Right VI		Epidermoid ca.
16	60	M	Pain in right orbit	Right II		Undiff. ca.
17	43	F	Partial deafness	Left V, IX, X, XII, Horner's		Sarcoma
18	57	M	Dysphagia	Right VII, IX, X, XII,		Epidermoid ca.
19	66	M	Nasal obstruction and epistaxis	Right XI		Undiff. ca.
20	65	F	Tinnitus and diplopia	Left II, V, VI	yes	Sarcoma
21	48	F	Pain in left neck and face	Left IV, V, VI, IX, X, XII	yes	Myeloma
22	58	F	Hearing loss, nasal obstruction, epistaxis	Left V	no	Undiff. ca.
23	49	M	Headache, diplopia	Right III, IV, V, VI, VII, IX, X, XI, XII	yes	Epidermoid ca.
24	60	M	Frontal headache, diplopia	Right III, IV, V, VI, VII, IX, X, XI, XII	yes	Epidermoid ca.

lationship of the fossa of Rosenmüller to the base of the skull. That fossa lies immediately beneath the foramen lacerum, permitting direct access for the intracranial extension of nasopharyngeal cancer. Figure 2 is a diagrammatic representation of an internal view of the base of the skull, showing the juxtaposition of the foramen lacerum and the third, fourth, fifth, and sixth cranial nerves.

MODE OF NEUROLOGIC INVOLVEMENT

Because of their particular location in the depths of the nasopharynx, these tumors may become quite sizable without producing any indication of their existence until some secondary structure is attacked.[7] We are concerned primarily when the nervous system is the object of this attack. As pointed out above, the cranial nerves in the middle fossa are most susceptible, particularly the fifth and sixth nerves, producing unilateral trigeminal pain and diplopia due to the lateral rectus palsy. As the tumor spreads forward, complete unilateral ophthalmoplegia and amaurosis may develop due to involvement of the third, fourth, and second nerves. The last four cranial nerves arise too far posteriorly to be involved intracranially in most instances; however, these may be and frequently are affected as they pass through the parapharyngeal space in proximity to the lateral nasopharyngeal wall. Figure 3 illustrates the frequency of various cranial nerve palsies in our series. Other than cranial nerve palsies, the neurologic sign most frequently seen is

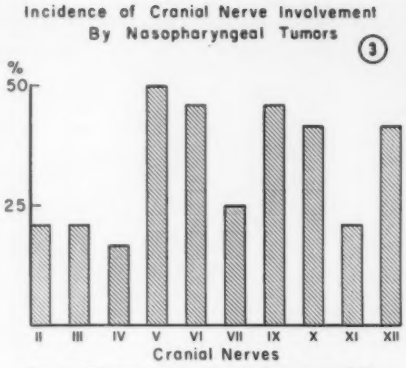


FIG. 3. Diagram illustrating the frequency of the various cranial nerve palsies in this series.

Horner's syndrome. This complication occurred in four instances in our series and is usually ascribed to compression of the sympathetic trunk as it enters the skull adjacent to the carotid artery. It may also be due to secondary involvement of the cervical sympathetic chain by a cervical lymph node metastasis. The least common neurologic complication is involvement of the spinal cord with the production of either a hemiplegia, as seen in three of our cases, or a paraplegia as a part of general dissemination, which occurred in one patient with epidermoid carcinoma.

DIAGNOSTIC CONSIDERATIONS

Steady unilateral facial or ear pain is the most common initial symptom of these tumors. This is trigeminal in origin and may simulate that due to a primary tumor of the gasserian ganglion. Therefore, in the presence of trigeminal pain either with or without palsies of neighboring cranial nerves, one should suspect the possibility of such a growth and both inspect the nasopharynx directly and palpate it manually. Any suspicious area should be biopsied. However, a negative biopsy does not exclude the diagnosis since we have seen as many as three negative results before a positive finding permitted a definitive diagnosis in one case of lymphoepithelioma.

Very recently a technic of obtaining exfoliated tumor cells from the posterior pharynx has been proposed.[8] This is done by using a simple suction cannula to obtain cells for cytologic examination. We have had no direct experience with this method to date, but the possibilities for its use are very interesting.

ROENTGENOGRAPHIC FEATURES OF NASOPHARYNGEAL TUMORS

Tumors of the nasopharynx may produce abnormalities demonstrable by conventional roentgenograms of the skull. These changes are not diagnostic in themselves, but may give important clues to the correct diagnosis. Jönnsen was able to detect the presence of 66 of 79 malignant tumors of the nasopharynx by the roentgenographic changes.[9] In the lateral skull film the two important abnormalities are the presence of a soft tissue mass in the nasopharynx and destruction of the floor of the sella turcica. Although the presence of a nasopharyngeal soft tissue mass is not uncommon during the first two decades, visualization and biopsy of the nasopharynx is always indicated in older patients (figure 4). Occasionally the tumor may be so much confined to one lateral wall that it is not seen on the lateral film, although it may be detected by anterior displacement of the soft palate. As these tumors extend through the base of the skull, they may invade the sphenoid sinus and begin to erode the floor of the sella turcica and the lower portion of the dorsum sellae. This produces a rather

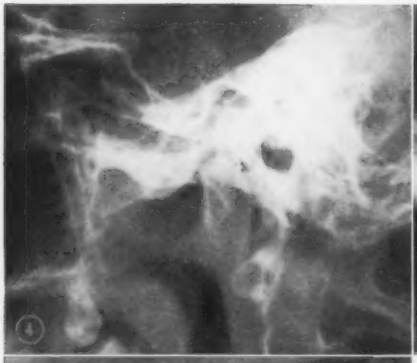


FIG. 4. Lateral roentgenogram of the skull in a 45 year old female with a sixth nerve palsy. Note the large soft tissue mass in the nasopharynx which proved to be a malignant tumor.

FIG. 5. Lateral skull film of a 65 year old male with an epidermoid carcinoma of the nasopharynx. Upward extension through the sphenoid sinus has resulted in destruction of the base of the dorsum sella and posterior half of the floor of the sella.

FIG. 6. Stenvers projection of petrous pyramid demonstrating destruction of petrous apex secondary to a nasopharyngeal cancer.

distinctive type of sellar deformity where the free portion of the dorsum is intact in the presence of destruction involving the base and the sellar floor (figure 5).

The submental-vertex or basal view of the skull is one of the most valuable projections in this disease, since destruction of the bony structures at the base of the skull may be demonstrated in a high percentage of cases. The structures more frequently involved are the mesial portions of the greater wings of the sphenoid, especially in the region of the foramen ovale. The petrous apex, basisphenoid, and pterygoid plates are also frequently involved (figure 6). A soft tissue mass may be seen in this view also.

The differential diagnosis includes excessive lymphoid tissue, usually found in the younger age groups but also observed in the fourth and fifth decades. This can be distinguished only by biopsy. Nasopharyngeal fibroma may be associated with a soft tissue mass in the nasopharynx and erosion of the bony structures at the base of the skull (figure 7). According to Jönnsen, the latter occurred in seven out of ten such cases. This tumor is practically limited to adolescent males and is never associated with neurologic signs. Solitary myelomas may occur in the upper respiratory tract and cause destruction of the surrounding bony structures (figure 8).

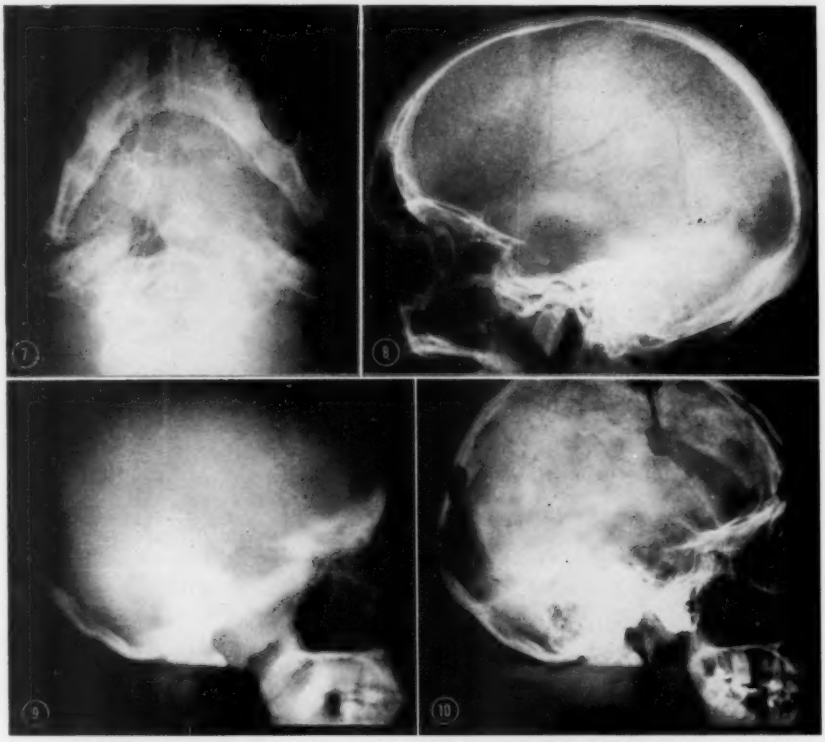


FIG. 7. Submental-vertex view of a 16 year old boy with a nasopharyngeal fibroma. Note erosion of pterygoid plates and floor of middle fossa. The cranial nerves were intact and the only symptoms were nasal obstruction and recurrent epistaxis.
FIG. 8. Lateral roentgenogram of the skull showing destruction of dorsum sella, floor of sella turcica, and clivus associated with a nasopharyngeal soft tissue mass that proved to be a myeloma.
FIG. 9. Lateral laminagram of the skull showing lobulated soft tissue mass in the nasopharynx.
FIG. 10. Same case as in figure 9, after opaque material was injected into an optic intrasellar tumor at the time of craniotomy. Note the inferior extension of the tumor into the nasopharynx.

Occasionally pituitary tumors or craniopharyngiomas may break through the sphenoid sinus and present in the nasopharynx as a soft tissue mass (figures 9 and 10).

In many of our patients with cranial nerve involvement due to nasopharyngeal tumors we were unable to demonstrate erosion in the base of the skull. Martin and Blady have shown that intracranial extensions occur in many instances by tumor growth through the foramina without destroying the skull.[2]

SUMMARY

Not infrequently a neurologist is first to diagnose malignancy of the nasopharynx. This stems from the fact that nearly one-half of these tumors involve the nervous system at some time during the course of the disease, and any earlier sign may be so obscure that the possibil-

ity of such a tumor is not considered. Neurologic symptoms, usually manifest by one or more cranial nerve palsies, may appear long before there are any signs of a primary lesion in the nasopharynx. Anatomic relationships of the structures involved in this disease, as well as diagnostic considerations and the radiographic findings from 24 cases of nasopharyngeal tumors, are reviewed.

Figures 1 and 2 are reproduced from Jackson and Jackson: "Diseases of the nose, throat and ear," W. B. Saunders Company, Philadelphia, 1945.

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■ We must now examine if the posterior and lateral columns have not a peculiar share in the transmission of sensitive impressions. As regards the posterior columns, the following experiments will show that there are conductors of sensitive impressions passing through them. Long ago I found that after a transversal section of the columns, the inferior surface of the section, that which seems no more to be connected with the encephalon, appears to be highly sensitive. I have since ascertained that the posterior roots in the neighborhood of that surface are the parts which then give the sensation of pain. But whether sensibility exists only in the roots or in the fibres of the posterior columns, it is a fact that pain is produced when this inferior surface is irritated. In 1852, I was led still more to admit that there are nerve-fibres coming from the posterior roots, and passing in two opposite directions in the posterior columns, some going upwards and some going downwards, or, in other words, some going direct towards the encephalon and some going away from it.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Compression of Spinal Cord and Cauda Equina in Achondroplastic Dwarfs

Joseph A. Epstein, M.D. and Leonard I. Malis, M.D.*

THE PURPOSE of this report is to draw attention to the neurologic abnormalities in achondroplastic dwarfs caused by protruding intervertebral disks compressing the spinal cord and cauda equina. Our recent experience in observing and treating an achondroplastic girl, 15 years of age with symptoms of a progressive myeloradiculopathy in the upper lumbar region of the spine, will be described. The only other child reported in this category was noted briefly by Spillane[1] who mentioned Poynton's patient, a boy of 15 who began to develop signs of spastic paraplegia at age 13.

The clinical findings are reviewed and the results of myelographic examination of the entire spinal canal illustrated in detail. The pathologic anatomy as it relates to disturbances in neurologic function is summarized in order to provide a more comprehensive understanding of the problem. Therapeutic measures are limited, and surgical decompression is the only effective treatment if carried out early in the course of the disease before irreversible changes occur.

CASE REPORT

A 15 year old girl first complained of pain in the lower thoracic and lumbar region of her back in November 1953. Pain was spontaneous in onset, of increasing severity, and about two weeks later radiated down the posterior aspects of both thighs to the knees and calves. Pain was persistent and was accentuated by movement such as bending, turning, and twisting. Bed rest provided partial relief. Coughing, sneezing, and straining did not affect the character of the pain. She gradually became aware of increasing weakness in her legs, with difficulty in walking, standing, and especially in climbing stairs. There were no changes in sensation or paresthesias. Bowel and bladder function was undisturbed.

Two weeks prior to her admission to Mount Sinai Hospital on January 20, 1954, pain became unusually severe and weakness in the legs had progressed to the point where she could no longer climb stairs or walk more than one block without distress.

Past history was noncontributory except that she had fallen backwards across the seat of a row boat in July 1953. There were no apparent sequelae. She had always participated actively and enthusiastically in school athletic activities until her present disability began.

On examination she presented a typical achondroplastic body habitus with a large head and trunk, short extremities, and prominent buttocks. She was 49½ inches tall, weighed 94 pounds, and her head measured 21¾ inches in circumference. Her spine presented an exaggerated lumbar lordosis, flattening at the lumbodorsal level with no evident gibbus deformity. There was weakness of both lower extremities, more pronounced in the proximal musculature. She was unable to climb the one step neces-

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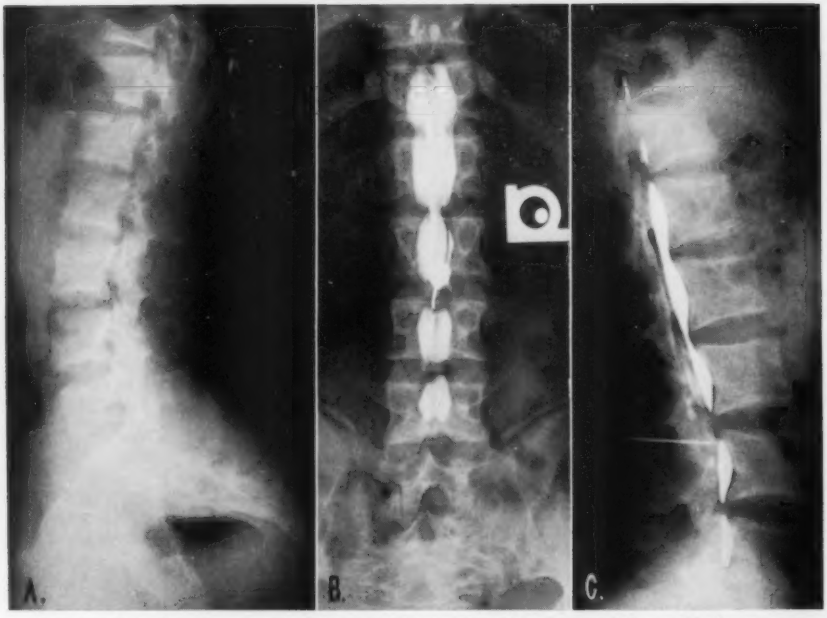

FIG. 1. *A.* Dorsolumbosacral spine showing anterior wedging of the bodies of the twelfth thoracic and first lumbar vertebrae with abnormally thick intervertebral disks, wedge-shaped in a reverse manner when compared with the vertebral bodies. *B.* and *C.* Myelogram showing interruption of the column of oil at the intervertebral spaces, the shallow spinal canal, and the scaphoid posterior surface of the vertebral bodies. Patient is horizontal. (Lumbarization of the first sacral vertebra and the unusually acute lumbosacral angle are evident.)

sary to get up on the examining table. While there was no evidence of spasticity, her gait was ungainly and waddling. Deep tendon reflexes were hyperactive and unsustained ankle clonus was elicited. A Babinski sign was found on the right, a neutral plantar response on the left. Reflexes were normal in the upper limbs. Superficial abdominal reflexes could not be elicited. Vibratory sensation was diminished in the toes of both feet. There were no other sensory abnormalities.

Roentgenograms of the spine disclosed four lumbar vertebrae with lumbarization of the first sacral vertebra and an unusually acute lumbosacral angle. There was anterior wedging of the bodies of the twelfth thoracic and first lumbar vertebrae (figure 1 A, C). The intervertebral disks in the lumbar region were thicker than normal and wedged at the dorsolumbar level in a reverse manner when compared with the vertebral bodies, straightening out this portion of her spine. The posterior surfaces of the lumbar vertebrae were unusually scaphoid, producing an undulating anterior profile in the spinal canal. This became more apparent on myelography (figure 1C).

Lumbar puncture was performed at the L2-L3 level. Spinal fluid was clear, colorless, and contained 20 mg. of protein. There were three lymphocytes per cc. of fluid. Manometrics were normal, with free rise and fall of the fluid on jugular compression. Six cc. of Pantopaque were injected. On fluoroscopy and spot films taken with the patient both horizontal and erect, it was apparent that the column of oil broke up at each interspace and presented a beaded appearance with coarse vertical striations typical of extradural compression of the roots of the cauda equina (figure 1B, C). With the patient erect the column of oil was held up

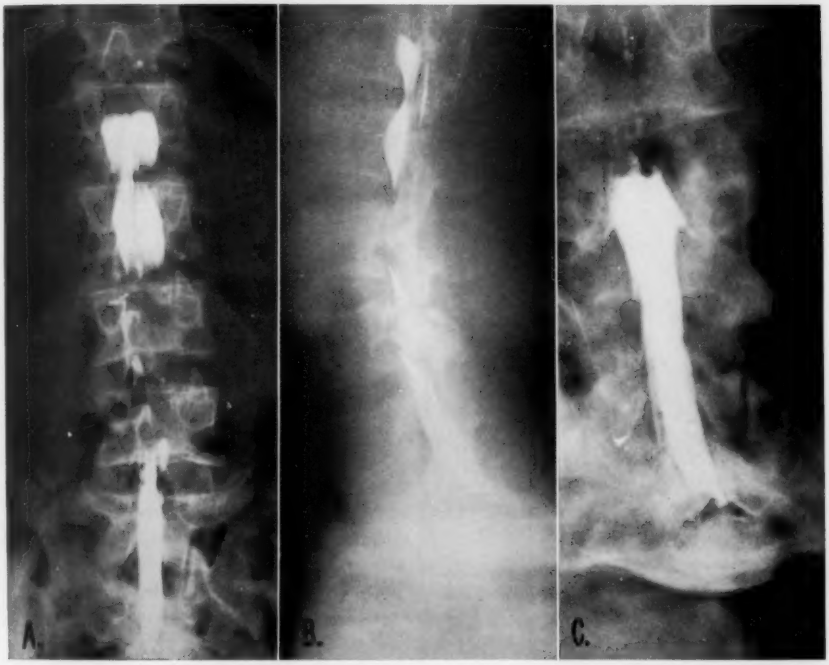

FIG. 2. *A.* and *B.* Myelogram with patient erect showing block at interspace between the second and third lumbar vertebra, partial at the interspace above. *C.* Postoperative film with patient erect showing all of the oil pooled in the caudal sac from which it was aspirated.

at the L1-L2 interspace, the block being complete at the L2-L3 level (figure 2A, B). Fluoroscopy repeated two days later did not disclose any alteration in this pattern. The oil present in the lower portion of the canal was noted immediately after injection with the needle at the L2-L3 level, the opening probably being situated at the site of maximum constriction and allowing oil to be injected both above and below this point. The transverse diameter of the dural envelope appeared normal. The spinal canal was unusually narrow in the anteroposterior diameter, and this is best seen in profile in figures 1C and 2B. The oil was permitted to flow up into the cervical canal. The column was interrupted at the intervertebral spaces in the thoracic spine as in the lumbar region, but not as pronounced (figure 3). No oil could be removed at this time.

As a result of these studies, it was felt that the clinical picture could best be explained by compression of the lowermost portion of the spinal cord, the conus, and the cauda equina at the upper lumbar levels, and that decompression by means of laminectomy was indicated. Operation was performed with the patient in the crouch position on January 26, 1954. The laminae in the entire lumbar region including the twelfth thoracic were removed. The laminae were unusually thick, up to 1.5 cm. in this diameter, and were removed with difficulty. The canal was remarkably shallow and, when unroofed, the dura pouted up into the space formerly occupied by the lamina under considerable tension. It did not pulsate. There was little or no epidural fat. At the upper lumbar levels where the block on myelography was noted, maximum constriction of the canal was found. Laminectomy was carried as wide as possible, care being taken to preserve

FIG. 3. Myelogram showing evidence of protruding disks interrupting the column of oil at the upper and midthoracic levels. The cervical canal is normal.

the articular facets. The dura was not opened. Extradural exploration lateral in the canal failed to disclose any evidence of extruded disk tissue and the procedure was terminated.

Postoperatively the patient had difficulty voiding and was placed on tidal drainage. Motor power improved perceptibly, and at the time of discharge from the hospital two weeks later she was able to walk without assistance. The Babinski sign could no longer be elicited at this time and the bladder function had returned to normal. By standing the patient erect, it was possible to repeat the lumbar puncture at the L5-S1 level and remove all of the previously injected Pantopaque (figure 2C). Fluoroscopy disclosed a free flow of oil through the entire canal.

Improvement since discharge from the hospital has been progressive. Pain in the back is no longer present. Six months after operation she was again able to climb stairs and walk three to five city blocks without weakness or distress. She returned to school and participated fully in all of her usual activities. One year after surgery, she was progressing normally in all respects. Neurologic examination was entirely negative. Movement of the spine was unrestricted despite the extensive laminectomy.

DISCUSSION

The clinical features of this case resemble those described in adults where signs of progressive compression of the spinal cord and cauda equina occur.[1–5] No clearcut and easily distinguished pattern of symptoms is apparent. Most common are severe back pain radiating into the lower limbs and the development of a progressive spastic type of paraparesis. When the condition is severe, total paraplegia with loss of bowel and bladder function results. Should the roots of the cauda equina be more severely compressed than the conus and adjacent cord, a lower motor neuron type of syndrome with foot-drop, absent reflexes, and muscular atrophy is found. Tingling followed by numbness in the feet and buttocks has been observed in varying degrees with all sensory modalities eventually becoming involved. The degree of neurologic abnormality shows fair correlation with the severity of compression found at operation and emphasizes the need for early diagnosis.

In the two cases reported by Schreiber and Rosenthal,[2] actual rupture of the disk into the spinal canal at the L2-L3 interspace occurred abruptly, the onset of symptoms appearing without warning in both. In the first patient, a 33 year old man, lifting while suddenly twisting his body was followed by giving way of both lower limbs, by pain in the back and legs, numbness, and tingling. In the second, a 31 year old woman, loss of bladder sensation, urinary retention, paraparesis, and sensory changes occurred suddenly unrelated to trauma. In both cases extruded fragments of disk

tissue were removed by laminectomy from the spinal canal with gratifying results.

On lumbar puncture varying degrees of manometric block are found.[1-3] This has been total in most cases, the fluid being xanthochromic and revealing protein values as high as 3,536 mg. per cent.[2]

Myelography in these patients presents a definite picture, with arrest and interruption of the column of oil at multiple levels.[1] Should the block be complete at a single level with no evidence of multiple lesions as in the cases of Schreiber and Rosenthal, it may be caused by an extruded fragment of disk tissue. This is especially true where there is a history of abrupt onset of symptoms. It is more common, as in this report and in cases of Spillane[1] and Vogl and Osborne,[3] to find segmentation of the oil column not only at the lumbar level but extending into the dorsal regions. The most severe compression, however, exists at the upper lumbar level where the greatest trauma to the cord and roots results.

In the achondroplastic dwarf predisposing factors exist which play a definitive role in the development of this entire picture. Primary is the remarkably narrow and shallow spinal canal (figure 4). Donath and Vogl[4] have indicated that this constriction is the result of a basic disorder of cartilaginous development, with alterations in the individual vertebrae of the entire spine. The decrease in the height of the vertebral body results in shortening of the spine, while shortness of the pedicles leads to marked constriction of the neural canal, greatest in the anteroposterior diameter. The thick pedicles are deformed by the premature synostosis of the centers of ossification of the body with those of the lamina. In adult achondroplastic dwarfs the canal is further narrowed by marginal exostoses protruding from the vertebral bodies and from the superior articular facets. The thickened laminae found at operation in the child presented have not been mentioned elsewhere. This is worthy of note, because it materially increases the difficulty of the operative procedure while contributing to the stenosis.

FIG. 4. Drawing of transverse section of a vertebra of an achondroplastic newborn infant (continuous line) and of a normal infant (dotted line), demonstrating the remarkable constriction of the neural canal in its anteroposterior diameter. (After Vogl and Osborne.[3])

The spinal cord develops normally. The space which the cord occupies in the spinal canal is disproportionately large at the expense of the subarachnoid and epidural spaces and accounts for the finding at operation of little or no epidural fat. In this manner, the cord also becomes more susceptible to trauma.

In the course of normal fetal development, the original "C" shaped configuration of the spine is gradually straightened by the growth of the cartilage cells in its longitudinal axis. The absence of normal cartilaginous development and growth in the achondroplastic fetus results in incomplete straightening of the vertebral column, the segments achiev-

ing the most normal structure being the upper dorsal and the lumbosacral. The lumbodorsal level is apparently the weakest link in the vertebral chain. It lacks the support of the thoracic cage and pelvic girdle and lags behind in its formation.[3] At this level wedging of the vertebral bodies occurs. Unusually thick, wedge-shaped intervertebral disks occupy the interspaces and, by their compensating action, enable the spine to present a straight profile. Where alterations are more profound, compensation is inadequate and dorsolumbar kyphosis develops. In its most severe state, collapse of the kyphotic portion of the spine occurs as the child attains the erect posture, with dorsal subluxation of the vertebral bodies and the production of an angular gibbus.[3,4]

It is not surprising that the contents of the spinal canal at this dorsolumbar level are so prone to injury. Because it is the weakest portion of the spine, deformed and poorly supported, it is not well equipped to withstand constant stress. This predisposes to early disk degeneration with progressive protrusion of the thinned out, bulging annulus into the canal and intervertebral foramina at multiple levels. Actual rupture of the annulus with extrusion and frank herniation of fragments of cartilage into the canal has been reported by Schreiber and Rosenthal. The former condition fortunately occurs more commonly, the multiple disk protrusions exerting pressure in a more gradual manner, slowly encroaching upon the contents of an already narrowed canal.

As in the child presented in this report and in the accumulated cases of Vogl and Osborne, laminectomy with adequate decompression of the spinal canal has provided relief of the compression syndrome, although no attempt has been made to decompress the canal along its anterior aspect. Extruded fragments of disk tissue lying free in the canal must, of course, be removed. The two patients with this syndrome presented by Spillane[1] were treated by laminectomy with extradural removal of massively protruding intervertebral disks at multiple levels. Unfortunately the details of the operative procedures are not given and it is not known whether the annulus had been ruptured in these cases. One patient, a man 40 years of age, was able to return to his former occupation, retaining good function of both legs. The second patient, a woman of 37, has progressed slowly, showing moderate improvement in only one lower extremity. Of interest is the finding of internal hydrocephalus in each patient, the suggested cause being shortening of the base of the skull, although no evidence of platybasia or of any deformity of the foramen magnum was discovered.

In the adult where a marked gibbus deformity of the spine exists, laminectomy confined to this region alone may be fruitless.[3,5] In these cases it is necessary to extend the decompression well above the level of deformity. As emphasized by Vogl and Osborne, postmortem examination in one of their patients revealed softening of the cord immediately above the angulated portion of the spine in the lower thoracic segment. Laminectomy had extended up to but not above this level of angulation and the softened portion of cord had not been decompressed. Osteophytes from both the vertebral margins and articular facets were of unusual prominence at this higher level, presumably a reactive osteoarthritis due to abnormal mobility of the spine. The histologic findings in the cord were in-

terpreted as a vascular myelitis secondary to local disturbance in blood supply.

SUMMARY

Herniation of intervertebral disks into the congenitally narrowed spinal canal of the achondroplastic dwarf is a not uncommon cause of compression of the spinal cord and cauda equina in these patients. Back pain with weakness progressing to paraplegia may result if surgical decompression is not performed before irreversible changes occur. Two clinical syndromes have been described. In the first, there is a gradual onset of symptoms caused by protrusion of multiple disks into the abnormally shallow canal. In the second, frank extrusion of a fragment of disk tissue occurs with an abrupt onset of severe disability. While spine films may show an exaggerated dorsolumbar kyphosis with alterations in the shape of the vertebral bodies and intervertebral disks, myelography is indispensable in defining the exact levels of compression. Simple laminectomy over multiple segments in the dorsolumbar and lumbar regions with preservation of the articular facets relieves the compression without interfering with the normal mobility of the spine. Extruded fragments of disk must be removed. If performed early as in the case reported, complete restoration of function is possible.

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■ I hope I shall be able to show, in one of the succeeding lectures, that the various sensitive impressions – of touch, of pain, of temperature, of muscular contractions, etc. – are transmitted by conductors which are quite distinct from one another, and so much so that the conductors of painful impressions, for instance, are not more able to convey other kinds of impressions than to transmit the orders of the will to muscles. This view appears to be positively established by pathological cases observed in man. I hope I shall now be allowed to make use of this view as if it were proved, and I will examine if the conductors of tactile impressions follow the same course in the spinal cord as those of painful impressions. I will, at first, relate experiments which seem to solve the following question: Do the conductors of tactile impressions proceed to the encephalon along the posterior columns, or do they pass into the gray matter as the conductors of impressions of pain?

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Treatment of Bell's Palsy with Cortisone and Other Measures

Madison H. Thomas, M.D.

BELL'S PALSY is a spontaneously occurring condition of unknown etiology in which function of the seventh cranial nerve is interrupted.

The paralysis of facial musculature is commonly accompanied by other changes in function which have been used as guides to the point of involvement along the course of the nerve. These include the presence or absence of pain, hyperacusis, taste on the anterior tongue, lacrimation, and changes in salivary secretion. However, the exact location of changes within the facial canal is less important than detection of adjacent cranial nerve involvement or demonstration of brainstem or supranuclear pathology. Total unilateral weakness, including the frontalis muscle, indicates a peripheral lesion, in contrast to the weakness of the lower face, tongue deviation, and pyramidal tract signs found in central pathology of strokes or tumors.[1] Further elaboration of differential possibilities is beyond the scope of this presentation. Over three-fourths of the cases of facial paralysis fall into the idiopathic variety and most can be recognized readily.[2,3] Nevertheless, it should be stressed that a complete neurologic examination is necessary to exclude other conditions from the one under consideration, Bell's palsy.

Numerous theories have been proposed to account for Bell's palsy. These include explanations based on specific infectious neuritis, vascular dysregulation with secondary ischemia, edema of the nerve or sheath, refrigeration, subclinical mastoid infection, and congenital stenosis of the facial canal as predisposing factors.[2–5] No one of these has been confirmed, nor have they led to any definite program of treatment of lasting significance.

Fashions of therapy of Bell's palsy have varied from surgical decompression[4] to doing nothing.[2] Analgesics are justified if pain is present. Other medications have included many supposed specifics as well as generally supportive agents such as thiamin and vitamin B_{12}, and while one of the latter is often given, it is done without much conviction. Vasodilatation with nicotinic acid, procaine, and so on has been generally ineffectual.

Heat may increase comfort. Massage,

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electrical stimulation, and splinting are commonly used and undoubtedly are quite helpful to the patient psychologically. Park and Watkins, in studying end results in 500 cases of facial paralysis, concluded that the course of the disease is not significantly altered by these physical therapies.[3] Treated or untreated cases had an almost identical pattern of recovery. Apparently, in the recovery phase of hyperactivity, there is sufficient activity to avoid contractures. In their study, muscle reeducation seemed helpful. Others[6,7] advise early physical therapy, but find recovery takes three to six months.

Protection of the surface of the eye from drying and foreign bodies requires varying technics from protective glasses to surgical closure.

Results of repeated stellate ganglion blocks have been encouraging in cases reported by Swan.[8,9] In one case some response appeared immediately. Full recovery took four to seven weeks in this group, but results are not uniform.[10] Further study of this method appears justified.

Surgeons have formulated varying criteria for decompression of the facial nerve. Since there is a four-fifths chance for recovery, it is now thought unwise to operate in the acute phase. Kettell advises waiting at least two months, but others believe surgery is contraindicated as long as spontaneous improvement is possible.[4]

Plastic repairs have been helpful as late reconstructive measures, but have no place in the management of the acute case. Anastomosis of the facial nerve to the accessory or hypoglossal nerve gives benefit in case of severe residual weakness after many months, but has disadvantages of unpredictability of results. In any event, none of the surgical measures are applicable if recovery can be effected during the acute phase of the paralysis by other means.

CORTISONE IN BELL'S PALSY

The first report of the use of cortisone in Bell's palsy was by Rothendler,[11] who observed recovery to begin in 48 hours and be complete in seven days after the start of treatment. We have had the opportunity to treat two cases with similar gratifying results.

Case 1.—A 22 year old male university student, without preceding illness or exposure, noted decreased closing of the right eye during the course of an evening and awoke the next morning with a complete right facial paralysis, without pain, hearing change, or loss of sensation or taste. On examination he showed no other abnormalities and was started on cortisone, 300 mg. per day in three divided doses, one day after onset of symptoms. He had previously been given facial massage and thiamin chloride, 100 mg. per day, and these were continued. He began to note improvement during the second day of treatment, and by the third day he could move the lip, close the eye, and lift the brow with effort. He was shifted to ACTH gel, 40 mg. per day, for the next ten days. He had a 90 per cent recovery in seven days, and complete recovery in 12 days.

Case 2.—A 63 year old male, previously well, developed a complete left facial paralysis over a period of several hours. Examination showed no other abnormalities. He was given thiamin chloride, 100 mg. per day, and no change whatsoever was noted for one week. He was then given 300 mg. cortisone per day in divided doses, and in less than 24 hours he was able to close the eye. Rapid improvement led to complete recovery in less than one week after cortisone was started.

This prompt response beginning in one or two days was in marked contrast to the delay of several weeks or months in cases previously seen.*

Bell's palsy is a relatively benign condition with eventual recovery expected in 75 to 85 per cent of cases.[2,3] Embarrassment and inconvenience are significant to the patient both during recovery and for the rest of his life if he develops facial spasm or is among the unlucky one-fifth who do not recover. Not only the incidence but rate of recovery are important, especially since the

*Since presentation of this paper, two additional cases of complete facial paralysis showed the same prompt response begining within 12 hours after cortisone (400 mg. per day) was started, with full recovery in less than two weeks.

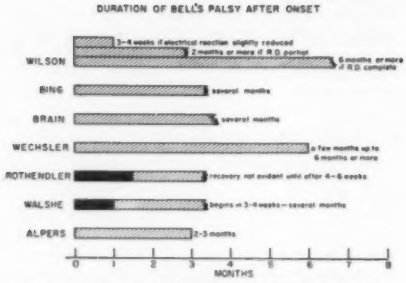

FIG. 1. Most authorities report intervals of several weeks before recovery begins (black areas) and several months for full recovery (shaded areas).

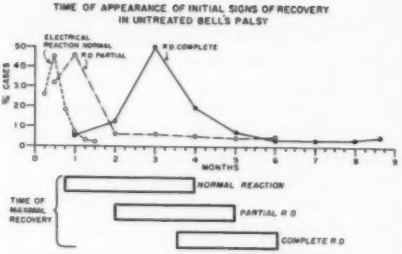

FIG. 2. In 250 cases reported by Park and Watkins,[3] initial signs of recovery were delayed from one week to over eight months. Earliest maximal recovery was in three weeks, with the average being three months.

earlier recovery begins, the more likely it is to be complete and uncomplicated.

Various authorities[5,13–17] have expressed their observations that recovery takes several months, as shown in figure 1. More specific information is provided by Park and Watkins[3] (figure 2) in a study of 500 cases of complete unilateral facial paralysis without specific treatment, 250 of which showed initial signs of recovery at intervals of one week to over eight months, depending upon whether electrical tests showed a normal response or a reaction of degeneration. The average time until appearance of initial signs of recovery was six weeks.

Maximal recovery was delayed an average of two months in cases of normal electrical response, four months in partial reaction of degeneration, and five months in complete reaction of degeneration. Earliest recovery was delayed three weeks and the average was three months from onset.

In our cases and most of those reviewed from the literature, [10,11,15,18–24] data are not available on the reaction of degeneration, but the above information provides a basis of comparison with the acute cases treated with cortisone.

The first important factor to consider is the delay in starting cortisone after onset of the paralysis. Figure 3 shows the results in six cases treated with cortisone when the paralysis had been present for ten days or more. No consistent benefit was seen in these cases, but no conclusions are justified because of the small doses of cortisone used in five of the six cases. The minimal changes reported would suggest trial of more adequate dosages in chronic cases, meanwhile withholding judgment until more information is available.

The results of more prompt treatment of 37 cases of Bell's palsy are shown in figure 4. Duration of symptoms in each case has been charted in comparison to the initial dose of cortisone (milligrams per day in divided doses). The effectiveness of cortisone in adequate dosage is apparent.

It is noteworthy that consistently better responses are related to the larger initial doses used. Below the 300 mg. per day level, results are much less consistent even though suggestively better than the com-

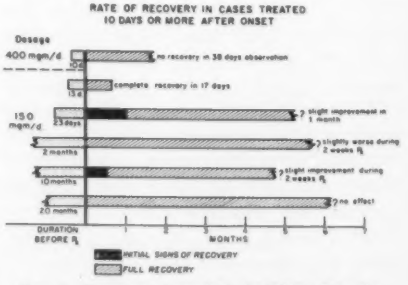

FIG. 3. Duration of paralysis is indicated to the left of the vertical line, and extent of persistence or observation after treatment to the right, showing no satisfactory response except in one case.

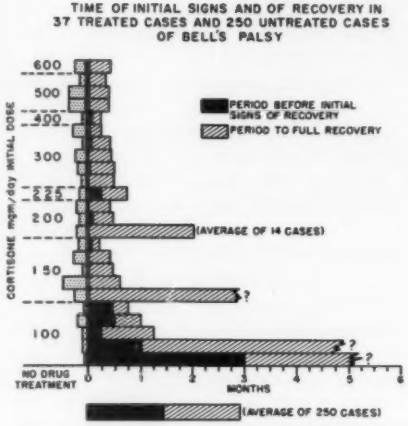

FIG. 4. Duration of paralysis is indicated to the left of the vertical line showing when treatment was started. Interval before recovery is shown to the right, compared to the average interval in untreated cases. Arrangement according to dosage used shows greater effectiveness of larger doses.

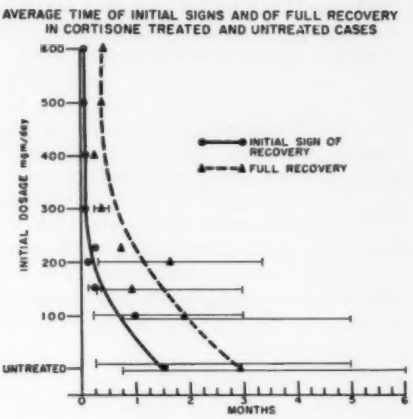

FIG. 5. Plot of dosage against recovery time again shows benefits of adequate dosage when compared to results in untreated or inadequately treated cases.

parison series. At 300 mg. or more per day, there is consistent recovery in 14 days or less, compared to the average of 87 days in untreated cases. Even more dramatic and impressive is the appearance of initial signs of recovery in one or two days after cortisone is started, in contrast to the average of 42 days observed in the untreated series.

The average time for appearance of initial signs of recovery and for full recovery has been charted against the initial daily dose of cortisone in figure 5. This simply emphasizes the highly consistent response of cases treated early and adequately, as compared to the slower, less consistent recoveries in cases treated with less than 300 mg. per day at the onset.

Statistical analysis of these data reveals the following: 1) The difference between the recovery rate in adequately treated cases (300 mg. per day or more) and in untreated cases would not occur by chance more than once in ten thousand times. 2) The difference between the adequately treated and inadequately treated cases (less than 300 mg. per day) would not occur by chance more than once in a thousand times (critical ratio 13.53). 3) There is no significant difference in result if treatment is started in the first nine days after onset.

Following the larger initial doses, it appears possible to decrease the level progressively depending upon the patient's response, but most authors report using cortisone for at least seven to ten days. Children's doses may be proportionately reduced.

The contraindications to the use of cortisone must be kept in mind.[25,26]

A peptic ulcer excludes its use, and in tuberculosis its use would be highly questionable. However, in the dosage needed for such short-term therapy, cortisone can be safely used postoperatively and in moderate hypertension or diabetes under control. As a precaution, 8 to 12 gm. of potassium chloride per day should be given orally, and the patient's weight, blood pressure, and general status watched. At the end of therapy, dosage should be tapered off from 100 mg. per day down to 10 or 15 mg. per day in decrements of 25 mg. per day or less.

Additional factors to be considered are the following: 1) Duration of treatment seems less important than adequacy of dosage in the first few days, but further data will be needed for a final conclusion as to how long therapy should be continued. 2) History of previous exposure or associated illness does not appear to be related to response to cortisone. 3) Location of seventh nerve pathology, indicated by symptoms of pain, hyperacusis, loss of taste, or change in secretory function, does not seem to be related to response to therapy. 4) Age, sex, or side of involvement are not significantly related to response.

SUMMARY AND CONCLUSIONS

1. Bell's palsy is an easily recognized illness, but before therapy is started the patient should be carefully examined to exclude other types of facial paralysis and other pathology.

2. The usual slow recovery and possible permanent disfigurement justify active, aggressive treatment if such treatment appears to be effective.

3. Surgical decompressive measures, plastic repairs, and nerve anastomoses are procedures of last resort and leave much to be desired in reliability and effectiveness.

4. From the data summarized above, oral cortisone appears to be an effective means of treatment if the following criteria are observed: Treatment must begin as soon as possible, at least in the first nine days. Treatment should be adequate; that is, minimum initial doses of 300 mg. per day for an adult, with gradual decrease over a seven to ten day period.

5. Further information should be collected on a larger number of cases of Bell's palsy treated with cortisone and related substances with varying dosage schedules to determine the optimum therapy under varying circumstances.

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Treatment of Muscular Dystrophy with Amino Acids and Vitamins

Stanley M. Wald, M.D. and Robert L. Lam, M.D.

SINCE THE INITIAL REPORT by Van Meter[1] in 1953 indicating significant subjective and objective improvement in ten patients with muscular dystrophy on a program of a vitamin-enriched protein hydrolysate, vitamin B_{12}, and folic acid, considerable interest has arisen in an evaluation of the efficacy of this treatment. This present study was initiated February 1954 to determine any actual beneficial effects which might arise in a series of patients given this therapy, in contrast to a parallel control series given placebos.

The well known chronic course of muscular dystrophy and its often unpredictable rate of progress make the evaluation of any therapeutic measure extremely difficult. Milhorat[2] has enumerated the numerous agents used unsuccessfully in the attempt to alter the progress of muscular dystrophy. The great diversity of these medications is partially explained by the fact that the pathogenesis of muscular dystrophy remains unknown. Specific drugs have been selected entirely on an empirical basis. The etiology of this obscure disease probably lies in the field of altered biochemistry of muscle modified by a hereditary factor. As yet, the paucity of facts illuminating this area of pathology precludes the intelligent correlation of the definite pharmacodynamic action of a preparation and its relationship to the disorder.

In a biostatistical study of a new medication in a chronic progressive disease of uncertain etiology, a degree of so-called improvement may occur in the series and may result in an unjustified interpretation that such medication was definitive in therapy. It is the opinion of the authors, therefore, that a placebo control is highly essential in order to maintain a state of single variable in every case: namely, the actual drug or drugs to be evaluated.

In the initial evaluation of a patient's maximum capacity, it must be pointed out that the patient may be functioning below his actual biologic level because of functional and organic disturbances associated with the chronic disability of a wasting disease. The patient's depression concerning his condition may lead to lack of motor activity, a greater sense of weakness, insomnia, anorexia, or bulimia. Inadequate supportive therapy on the part of family and physician may result in poor general health,

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cachexia, obesity, and even disuse atrophy of relatively less dystrophic musculature. The patient's enthusiasm and optimism under a new treatment program may subconsciously aid in correction of the disturbances which had previously caused performance at a submaximal degree. The use of a double blind experimental profile corrects this possible error in clinical evaluation. Leslie[4] has recently emphasized the value of placebo controls in this regard.

In addition to the pitfalls commonly encountered in establishing a fundamental baseline in each patient, the usual course of the particular disease studied must be kept in mind since spontaneous remissions or halting of progression may occur. This may be true in muscular dystrophy.

Van Meter reported striking objective and subjective improvement in a series of ten patients who had received the protein hydrolysates and vitamins for a period of time ranging from two months to one year. The patients were noted to have improved in one or more of the following ways: return of strength, restoration of normal respiratory action, increase in size and tonus of atrophic muscles, and relief of depression. The patients claimed to have gained a sense of well-being, body warmth, and an increase of strength.

One year later Drew and co-workers[3] reported their findings in a series of 42 muscular dystrophy patients who had been given this treatment from five to seven months. At the end of this time none of these patients was credited with objective improvement. Several of them did experience subjective improvements similar to those reported by Van Meter. The conclusion of this study was that the treatment was ineffective.

PROCEDURE

Thirty-three muscular dystrophy patients, who had been examined at least once within the previous year, were used to evaluate treatment. The patients were divided at random into two groups, a treatment group receiving the protein hydrolysate and vitamins, and a control group receiving placebos. There was approximately equal distribution in each group according to sex, age, extent of involvement, and type of dystrophy.

MEDICATIONS

Protein hydrolysate

Amino acid produced by enzymatic digest of casein	16.0 gm.
Ascorbic acid	100 gm.
Thiamine hydrochloride	10.0 mg.
Riboflavin	6.0 mg.
Pyridoxine hydrochloride	1.0 mg.
Calcium pantothenate	1.0 mg.
Niacinamide	50.0 mg.
Vitamin A	5,000 USP units
Vitamin D	500 USP units
Iron peptonate	0.1 gm.
Tribasic calcium phosphate	1.0 gm.

Vitamin

Vitamin B_{12}	50.0 μg.
Folic acid	3.34 mg.

Placebo powder

Brewer's yeast powder, flavored with beef bouillon cubes and celery salt.

Placebo capsules

Lactose

The treatment series received a supply of the protein hydrolysate and vitamins dispensed in the following manner: one heaping teaspoonful of the protein hydrolysate mixed with liquid or solid foods, taken with meals three times a day, and one capsule of vitamins to be taken both morning and evening.

The control series received a yeast powder and lactose capsules identical in appearance to those given the treatment group, and given in similar amounts. All patients believed they were receiving the new medication of which they had read or heard.

One patient withdrew from the study; two did not provide sufficient data for us to include them. Tables 1 and 2 give data on patients who continued on the program until completion.

Before receiving medication each patient had been given a thorough physical and neurologic examination. Deformities, amount of muscle wasting, and limitation of move-

TABLE 1
CONTROL GROUP

	Sex	Age	Type	Atrophy	Creatinine excretion Before mg./24 hr.	% Total	Creatinine excretion After mg./24 hr.	% Total	Muscle strength Before	After	Subjective opinion
1.	M	3	Juv.	2+	185	40.8	188	48.9	3324	3480	little stronger
2.	M	7	P.H.	1+	235	43.1	202	40.4	3115	3060	falls less frequently
3.	F	7	Juv.	2+	119	35.0	121	33.2	2705	2540	no change
4.	F	8	P.H.	1+	205	33.0	245	30.2	2955	3145	can raise up from stooping without hands
5.	M	9	P.H.	2+	428	53.6	116*	40.0	3185	3235	medicine is no good
6.	M	10	P.H.	2+	414	36.0	444	49.0	2535	2335	no change
7.	M	11	P.H.	2+	144	24.5	193	20.6	2765	2550	no change-neck stronger
8.	M	11	P.H.	2+	145	22.0	130	18.4	1910	2240	no change
9.	M	11	P.H.	2+	390	42.8	164*	33.0	2165	1645	generally poorer
10.	M	12	P.H.	2+	189*	63.0	273*	60.4	1805	1600	no improvement-arms weaker
11.	M	12	Juv.	3+	157	20.0	211	27.1	1570	1565	no change
12.	M	13	Juv.	2+	252	42.0	230	37.7	1290	1170	contractures worse
13.	M	13	P.H.	2+	522	45.8	410	56.6	3010	3170	greater endurance, contractures improved
14.	F	23	FSH	1+	648	64.0	650	72.2	3790	3845	no noted change
15.	F	55	FSH	1+	546	68.4	576	67.4	3400	3560	no change

TABLE 2
TREATMENT GROUP

	Sex	Age	Type	Atrophy	Creatinine excretion Before mg./24 hr.	% Total	Creatinine excretion After mg./24 hr.	% Total	Muscle strength Before	After	Subjective opinion
1.	M	5	P.H.	2+	205	36.7	210	28.9	—	—	getting worse
2.	F	8	Juv.	2+	190	27.8	247	39.0	2705	2295	no change
3.	M	9	P.H.	1+	236	48.6	155	36.4	3245	3345	no change
4.	M	9	P.H.	2+	220	45.7	230	48.5	2500	2090	more alert-gets around better
5.	M	11	Juv.	3+	223	21.5	98*	27.3	1670	1775	no change
6.	M	11	P.H.	3+	189	32.1	118*	21.6	2555	2110	somewhat stronger
7.	F	11	Juv.	1+	610	52.6	662	50.0	3415	3405	increased weakness in left thigh
8.	M	12	Juv.	2+	148	20.7	198	23.6	1830	1875	no change
9.	M	14	P.H.	1+	423	49.4	468	60.0	3160	3170	falls less frequently
10.	M	24	P.H.	2+	320	34.8	300	32.0	1880	1900	no change
11.	M	24	FSH	3+	540	34.0	530	34.3	2500	2485	can't walk as well
12.	F	26	FSH	1+	714	56.2	575	49.2	3095	3360	falls more often
13.	M	28	FSH	3+	371	43.2	224	34.0	2385	2280	no change
14.	M	29	Juv.	2+	352	25.0	416	26.2	2270	2110	not much stronger
15.	M	45	FSH	1+	780	55.0	890	54.0	3165	3535	walks faster

ment imposed by contractures were noted. Ability of various muscle groups (for example, flexors of forearms or extensors of legs) to perform against different degrees of resistance was scored on muscle charts.

Since it is believed that creatinine excretion is a measure of the active muscle of the body, any improvement in muscle function should be accompanied by an increased excretion of creatinine. On the other hand, creatine excretion would be expected to increase when precursors of creatine are fed to patients with muscular dystrophy, as has been shown when they have been fed glycocyamine and betaine. The creatine may be either increased or lowered with no changes in creatinine excretion. Increased creatinine excretions would have more critical value in indicating improvement (tables 1 and 2). Since none of the patients was hospitalized the urine collections were not always complete, which can be seen from the volume of urine recorded. Obviously incomplete collections are marked in the tables. Creatinine is reported in mg. per 24 hours and in per cent of the total creatinine plus creatine. The latter value would be uninfluenced by faulty collection.

These examinations and laboratory studies were repeated at approximately three and again at six month intervals. The patients and their families were questioned about subjective changes in disabilities common to muscular dystrophy at all examinations. Frequency of falling, ability to perform given tasks, ease in arising and turning the trunk were among the factors considered an index of the patient's general status.

RESULTS

There was no significant objective improvement in actual muscle strength in either group. No patient regained new ability to walk or to perform tasks formerly impossible. Some reported less frequent falling. No change in deformity or decrease in contractures were noted.

Minor subjective improvement of a general nature, such as an increased sense of wellbeing, increased appetite, decreased incidence of respiratory infection, was reported with greater frequency by those in the treatment group.

There were a few cases showing some increase in percentage of creatinine excretion in both the control and the treatment series. The changes were not above 10 per cent and occurred with equal frequency in both groups. There were no dramatic changes in creatine excretion under this treatment.

CONCLUSION AND SUMMARY

Clinical evaluation of the Van Meter treatment for muscular dystrophy, consisting of amino acid, folic acid, and vitamin B_{12}, indicated no significant improvement in muscle performance in a series of patients studied with a control group. In addition, the Van Meter treatment did not alter the biochemical abnormalities of creatinine and creatine excretions in the urine of patients with muscular dystrophy.

Therefore, it is the authors' opinion that treatment of muscular dystrophy with amino acid, folic acid, and vitamin B_{12} is of no value, either in a definitive or symptomatic sense.

We wish to acknowledge the work of Dr. Ethel Ronzoni for the creatine and creatinine determinations and Meredith Holekamp for her technical assistance.
The medications used in this program were provided by Walker Laboratories of Mt. Vernon, New York, and E. R. Squibb and Sons.

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■ If we divide transversely a lateral half of the spinal cord in two places, so as to have three pairs of nerves between the two sections, we find that the middle pair has almost the same degree of sensitivity as if nothing had been done to the spinal cord, while the two other pairs have a diminished sensibility, the upper one particularly in its upper roots, and the lower one in its lower roots: which facts seem to show that the ascending fibres of the upper pair, and the descending fibres of the lower one, have been divided before they had made their decussation.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

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DECEMBER, 1955

Toward a National Program For Training Neurologists Because of the recent surge to national proportions of graduate training programs in clinical neurology, an achievement in which the history of the AAN is inseparably fused, this issue of the Newsletter is devoted to a sketch of these developments toward a national program for training neurologists.

The Situation After the War At the close of World War II, many authorities considered existing programs for the teaching of medical neurology in the United States as sorely splintered and depleted. So grave was the neurologists' concern for the fate of neurology, that the problem provided the central theme for five presidential addresses in as many years before national neurologic societies. Their prevailing tone often stressed a dire need for added teaching facilities and opportunities in neurology to attract more young men to this field.

VA and AAN Programs Spearhead Action In the late 1940's, while this problem was being debated, at least two new events emerged sounding a more progressive note. First came the establishment of new neurologic training centers under the Veterans Administration for the large number of neurologically disabled veterans. Affiliated with medical schools, these centers opened new vistas for training in neurology (the VA now sponsors 29 residency programs in neurology). Second, the American Academy of Neurology was created in 1948, and its committees immediately began programs to consolidate the "splinters" in neurology; to rejuvenate the field with new, young blood; and to plan for the organization of a more definitive identity for clinical neurology in American medicine.... The establishment in 1949 of A. B. Baker's postgraduate review courses in neurology as an integral part of the annual Academy meetings will remain as a permanent monument to these early efforts toward the development of a national program for the training of neurologists.

Experimental Neurology Adds Impetus While these enterprises were gaining momentum, impetus was added from another field--the expanding field of experimental neurology where laboratory scientists were gaining new knowledge, developing new technics, even new disciplines. These growing programs needed more support not only for their research activities, but also for training more scientists to man their prom-

ising projects, and for more clinical investigators to test and apply laboratory discoveries to the clinic.

Voluntary Agencies Create Public Awareness Coupled with these professional developments, and in a national climate of shifting emphasis from acute to chronic disease, were the pleas of crippled neurologic patients, their relatives, and friends who saw for the first time an opportunity to press for aid for their afflictions, which for centuries had been synonymous with shame and despair. The response to their pleas was embodied in the formation of new voluntary health agencies dedicated to research, training, and care programs in neurologic diseases.... An outgrowth of these "pooled" efforts was additional public support for neurologic research and training from all sources, both voluntary and governmental. Part of this increased public support was provided by the growing grants programs of the National Institute of Neurological Diseases and Blindness.

NINDB Training Programs in Neurological Disorders The purpose of the training programs of the National Institute of Neurological Diseases and Blindness (established in 1950) is to complement its national research effort by increasing the present number of clinical neurologists, ophthalmologists, and allied scientific personnel who wish to pursue an academic or research career. These programs developed slowly at first, in fact, assumed no significant magnitude until 1953 when new funds were first made available for Graduate Medical Training Grants in neurologic and sensory disorders to universities and other nonfederal institutions. Since 1953 this Graduate Medical Training Grants Program has been increased substantially each successive year, and together with a program in Graduate Clinical Traineeships and in Research Fellowships comprise the Institute's present total training grants program.

Present Number and Dispersion of Graduate Training Grants Operating under a set goal of aiding medical schools and hospitals to initiate, improve, or expand projects designed to train teachers and clinical investigators in neurology, grants are currently being supported in 40 medical schools or hospitals in many key geographic centers in the United States. Among the universities now receiving grant awards are Baylor, Buffalo, California, Chicago, Colorado, Columbia, Cornell, Emory, Georgetown, Harvard, Indiana, Iowa, Johns Hopkins, Kansas, Louisiana State, Louisville, Maryland, Michigan, Minnesota, New York University and State University of New York, North Carolina, Northwestern, Oklahoma, Oregon, Pennsylvania, Tennessee, Utah, Vermont, Washington (St. Louis), Washington (Seattle), Western Reserve, and Yale. In addition, the following institutions are receiving similar grant awards: Medical College of Alabama, Albany Medical College, Bowman Gray School of Medicine, Minneapolis General Hospital, Montefiore Hospital

(New York City), Mount Sinai Hospital (New York City), and Tufts College Medical School.

Amount, Distribution, and Period of Awards The amount of training grant funds awarded to any single institution varies widely in relation to individual program needs. In general about 75 per cent of all funds under the Graduate Medical Training Grants Program are utilized for the support of teaching and resident personnel, usually as salaries for instructors and stipends for residents; approximately 17 per cent is used for equipment, consumable supplies, and meeting travel for residents in training. The remaining 8 per cent is used by the grantee institution for overhead and other indirect costs.... Awards to institutions initiating new programs are, as a rule, for a period of two or three years. Expanding but established programs, or new programs reaching maturity and acquiring residency approval, often receive awards for a five year period to provide maximum stability. Prior to the termination of an award any institution may apply for a renewal of a grant.

Program Productivity While the Graduate Medical Training Grants Program is currently only in its second full year, as a growing project which requires at least five years for any definitive evaluation, yet certain preliminary spot observations already have been made: a general improvement in the quality of neurologic training; 50 per cent more neurologic residents in training; and more than 100 per cent increase in the number of medical schools having established graduate training programs in neurology.... Of the 40 graduate training programs in neurology, 28 have rather well established graduate training programs as compared to ten or 12 a few years ago. Of these 28 medical schools with established programs, 74 residents have been added to their staffs, an average of 2.5 residents per school.... Already, 26 neurologic teachers, who have received part of their training under the NINDB programs, have taken positions in other medical schools, including 18 instructors, seven assistant professors, and one full professor.

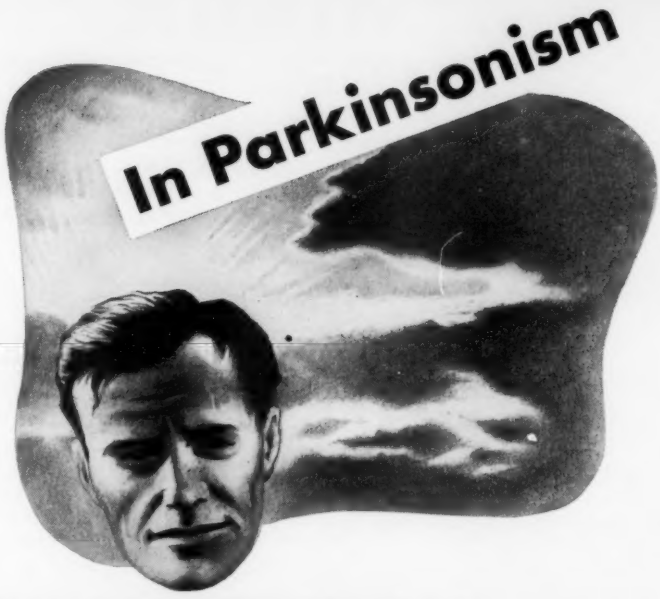
How to Apply For a Training Grant A designated program director of a neurologic training activity in a medical school or hospital completes a standard application form, obtainable upon request to NINDB. The completed application, which must be sponsored by the training institution, is then assigned for review by a training grants committee composed chiefly of leading neurologic educators and scientists in universities. This committee assesses the competence of the applicant and the merits of the proposed program. Its recommendations then are transmitted to the National Advisory Neurological Diseases and Blindness Council for final consideration. Following council recommendations, the Surgeon General of the Public Health Service approves or disapproves the application. If the decision is favorable, NINDB processes the payment of

funds to the training institution, which in turn allocates them to the director of the program.... Training grant applications may be submitted at any time. The usual lapse between receipt of application and payment of grant is three to four months.... All requests for application forms or inquiries concerning the Graduate Medical Training Grants Program should be addressed to the Chief, Extramural Programs, National Institute of Neurological Diseases and Blindness, Bethesda 14, Md.

Training Grants Committee Holds Planning Conference A subcommittee of the NINDB Training Grants Committee, A. B. Baker, chairman, convened in Minneapolis (Nov. 16), with Gordon Seger, Chief, NINDB Extramural Programs, to formulate plans for a future conference of directors of all programs aided by neurology training grants. This future conference will be held at the AAN annual meeting in St. Louis (April 23-28, 1956). Purpose of the conference is to further acquaint potential program directors with policies and procedures of the NINDB training grants program and provide group discussions of problems encountered in the training of neurologists.

Graduate Clinical Traineeships and Research Fellowships Rounding out the NINDB total training program and adding to its flexibility are the programs in Graduate Clinical Traineeships and Research Fellowships. The former is designed to provide, both here and abroad, advanced training to neurologists in special clinical or basic science fields, such as EEG, neuropathology, rehabilitation, and also supply a means for neurologic training to physicians in other medical specialties interested in diseases of the nervous system, such as internists, pediatricians, psychiatrists, and physiatrists. This program provides annual stipends, usually of a year's duration, to approved applicants. To date, 87 physicians have been awarded this specialized training. Applications for clinical traineeships are reviewed by the NINDB Traineeship Review Board which meets at least three times a year or more, depending on the urgency of the applications.... The purpose of the Research Fellowship Program is to aid, through the award of individual stipends, promising young scientists (predoctoral and postdoctoral) who have demonstrated an interest and competency in research, to add to their academic training and research experience. The program provides a growing pool of research manpower proved to be of value to the pursuit of neurologic research and training of neurologists in the basic sciences. Of those trained so far, 75 per cent have elected to remain in research or teaching. Applications for research fellowships may be submitted at any time, and they are evaluated by the NINDB Fellowship Specialty Board, which meets at regular intervals.

Robert Bailey



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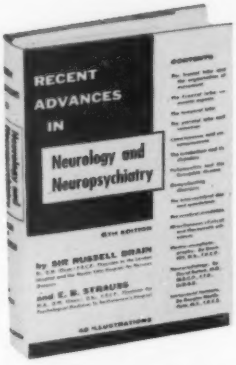

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